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DRY WEIGHT ASSESSMENT AND CARDIOVASCULAR IMPACT IN HEMODIALYSIS PATIENTS

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DRY WEIGHT ASSESSMENT AND CARDIOVASCULAR IMPACT IN HEMODIALYSIS PATIENTS

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List of abbreviations

ANP: Atrial natriuretic peptide
BIA: Bioimpedance analysis
BNP: Brain natriuretic peptide
CVP: Central venous pressure
ECW: Extracellular water
ESKD: End stage kidney disease
IDWG: Interdialytic weight gain
IVC: Inferior vena cava
LVEF: Left ventricle ejection fraction
LVH: Left ventricle hypertrophy
NT-proBNP: N-terminal pro-B-natriuretic peptide
NYHA: New York Heart Association
RBV: Relative blood volume
TAFO: Time averaged fluid overload
TBW: Total body water

Abstract

Cardiovascular events represent the major cause of death among hemodialysis patients. Volume overload is common in this population and is one of the most important prognostic factors determining the outcome. It is associated with high blood pressure, left ventricular hypertrophy, pulmonary hypertension, increased risk of heart failure, arrhythmia, hospitalizations and mortality. Determining and achieving a dry weight pose one of the greatest difficulties in the therapy of these patients.

The pillar of dry weight estimation is clinical evaluation but there is high demand for more objective measures of fluid status. The aim of this study was to evaluate and compare the different methods, techniques and medical devices used for dry weight assessment and their impact on the cardiovascular morbidity and mortality in hemodialysis patients.

We concluded that bioimpedance is currently the most promising method and its use is already widespread. There is still the need for standardization and reproducibility of this fluid status approach and its impact on reducing cardiovascular events remains unclear. The benefits and harms of probing dry weight should be tested in qualified large long-term randomized trials. Avoidance of aggressive dry weight management, as well as the promotion of tolerability of symptoms and hemodynamic stability should be a priority for reducing cardiovascular events.

Keywords: hemodialysis; dry-weight; volume overload; cardiovascular disease; mortality

Resumo

Os eventos cardiovasculares representam a principal causa de morte nos doentes em hemodiálise. A hiperhidratação é frequente nesta população e é um dos fatores prognósticos mais importantes. Está associada ao desenvolvimento de hipertensão arterial, hipertrofia ventricular esquerda, hipertensão pulmonar, risco aumentado de insuficiência cardíaca, arritmia, hospitalizações e mortalidade. Determinar e manter o peso seco é um dos maiores desafios terapêuticos nestes doentes.

A avaliação clínica constitui a base da determinação do peso seco, mas existe a necessidade de definir métodos objetivos para quantificação do estado de hidratação. O objetivo deste trabalho é avaliar e comparar os diferentes métodos, técnicas e dispositivos médicos usados para determinação do peso seco, bem como analisar o seu impacto em termos da morbilidade cardiovascular e mortalidade em doentes em hemodiálise.

Concluiu-se que a bioimpedância é atualmente o método mais promissor e o seu uso já se encontra difundido, mas existe ainda a necessidade de introduzir uniformização e reprodutibilidade na abordagem ao estado de volémia destes doentes e o seu impacto na redução de eventos cardiovasculares ainda se encontra por esclarecer. Os benefícios e riscos da determinação rigorosa do peso seco devem continuar a ser testados em grandes estudos randomizados de longa duração. Evitar uma gestão agressiva do peso seco, bem como a promoção da tolerabilidade dos sintomas e da estabilidade hemodinâmica devem ser uma prioridade para a redução da morbilidade cardiovascular.

Palavras-chave: hemodiálise; peso seco; hiperhidratação; doença cardiovascular; mortalidade

1. Introduction

Chronic kidney disease is common in the general population and it is estimated that there are approximately 3 million patients with end stage kidney disease (ESKD) in the world.[1] Life quality and expectancy in ESKD is notoriously impaired and depends on the efficacy of renal replacement therapy. There are currently four treatment options for ESKD patients: hemodialysis, peritoneal dialysis, renal transplantation and conservative care. For various demographic, clinical, and logistical factors, hemodialysis is currently the most prevalent therapy worldwide.

According to the Portuguese Registry of Dialysis and Transplantation,[2] 2634 new patients started dialysis or were submitted to renal transplantation during 2018, 2378 (90,3%) of which opted to start hemodialysis. During 2018, 12227 patients were being treated by hemodialysis and diabetes and hypertension were the main causes of ESKD. The major death cause among these patients was cardiovascular, followed by infection non related with vascular access, malignancy, sudden death and cachexia.

Hemodialysis is a life saving treatment for ESKD patients but when starting hemodialysis, cardiovascular mortality is 8.8 times higher than the general population.[3] Traditional and non traditional cardiovascular risk factors do not entirely explain why cardiovascular disease represents the most important cause of death in chronic hemodialysis patients. These risk factors can be associated with the primary kidney disease, patient's habits and personal medical history,[4] but also related to hemodialysis treatment modality and technique. Hypervolemia in hemodialysis patients is a known prognostic factor, associated with impaired oxygenation, end-organ damage, morbidity and mortality.[5] Besides optimizing cardiovascular risk factors, there is a need to modify dry weight approach and optimize fluids status assessment.

Since the implementation of hemodialysis in 1960s, technological improvements have not been equally followed by improved survival. Research towards optimal estimation of dry weight has been ongoing for many years but there is still no formal method or protocol widely accepted. Each method has its strengths and limitations. Apart from clinic assessment, the most used and increasingly validated approach is bioimpedance analysis (BIA) but there is still the need for validated tests and markers for volume status and dry weight determination. Prospective, multicentre trials have failed to demonstrate clinical effectiveness in order to standardize procedures and prevent cardiovascular morbidity and mortality.

The aim of this study is to evaluate and compare the different methods, techniques and medical devices used for dry weight assessment and their impact on the cardiovascular morbidity and mortality in hemodialysis patients.

2. Methods

2.1. Search strategy

We performed an electronic search of the MEDLINE (1950-2018) and EMBASE (1980-2018). We used comprehensive free text and MeSH synonyms for hemodialysis, dry-weight, volume overload, cardiovascular disease and mortality. We searched only published articles, and placed no restrictions on time or language of publication. For included articles, reference lists and the “related articles” function on PubMed (www.pubmed.gov) were also assessed for possible inclusions. We supplemented searches by checking references cited in published systematic reviews and by reference to the bibliographies of the articles extracted from the literature reviews.

2.2. Study selection

We selected articles that: included hemodialysis patients submitted to a dry weight assessment method, included any cardiovascular outcome, and were randomized, quasi-randomized trial or clinical trial.

3. Importance of volume control

Hemodialysis is incapable of replacing all the physiological kidney functions and its intermittent nature is a clear example of this limitation. Fluid retention and increased extracellular water (ECW), as reflected in a body weight gain between sessions, explain why volume status and dry weight are closely related. The necessary fluid removal is obtained by ultrafiltration in order to achieve a dry weight.

Volume overload is one of the most common complications in ESKD and depends on fluid and sodium intake, residual kidney function, cardiovascular function, dialysate concentration and ultrafiltration rate. It also seems to be an important contributor for maladaptive mechanisms like myocardial remodelling, that combined with other risk factors is responsible for left ventricular hypertrophy (LVH), subendocardial ischemia and myocyte death.[6] In hemodialysis patients this is associated with adverse outcomes including high blood pressure, pulmonary hypertension, vascular stiffness, and increased risk of heart failure, arrhythmia, hospitalizations and mortality.[7–9]

Argwal et al.[10] confirmed the importance of volume control in treating hypertension by recruiting 150 chronic hypertensive hemodialysis patients, who had their dry weight prescribed by clinical judgment without increasing the frequency or duration of dialysis. The intervention group received progressive reduction of dry weight with additional ultrafiltration. In the 8 weeks of trial, after significantly reducing dry weight for an average of 1 kg, the blood pressure of the intervention group changed -6.6/3.3 mmHg. The improvement in blood pressure was reported to be well tolerated and more effective than an antihypertensive drug.

Wizemann et al.[7] concluded that overhydration determined by bioimpedance was an independent risk factor for mortality and Hur et al.[11] showed that adjusting dry weight and fluid removal based on assessment of fluid overload lead to regression of left ventricular mass index in the intervention group after a 1 year follow-up.

On the other hand, volume depletion is associated with uncomfortable symptoms for the patients and intra-dialytic hypotension, which is a cause of cardiovascular events and mortality in patients undergoing hemodialysis.[12,13] Dialysis patients already combine a large variety of mechanisms and conditions that predispose to functional and structural cardiovascular abnormalities. In addition, hemodialysis itself works as an acute stress factor that may lead to cardiac injury by precipitating subclinical ischaemia. The phenomenon that leads to ischaemia is related to the ultrafiltration rate and hemodynamic stability during the hemodialysis session. Prolonged cardiac dysfunction, known as myocardial stunning, can result in heart failure and be a trigger to arrhythmias.[14,15] It has been already demonstrated that patients with evidence of myocardial stunning had increased relative mortality after a 12 months follow-up.[14]

It is important to underline that both overhydration and volume depletion are associated with deleterious consequences in patients undergoing hemodialysis.

4. Dry weight definition and management

Achievement of a normal hydration state is one of the most important goals of hemodialysis treatment, hence dry weight should express the weight of the patient close to euvolemia. Several definitions for dry weight have been proposed through the years and the practice varies among nephrologists. The earliest definition found in literature relies on blood pressure and its reduction to hypotensive levels during ultrafiltration.[16] Over the years other definitions have been proposed[17,18] and the idea of avoiding symptoms has been promoted. Currently, one of the most accepted definitions is related with the lowest tolerated post-dialysis weight.[8]

Establishing a dry weigh is necessary in each hemodialysis session prescription for the calculation of ultrafiltration rate. This is traditionally achieved by using clinical trial and error methods that do not account for nutritional status and lean body mass changes. Agarwal et al.[19] suggested that there are also potential risks associated with probing dry weight like increased risk of thrombosis of the vascular access, loss of residual kidney function, as well as intra and interdialytic hypotension.

Ultrafiltration allows fluid removal from the intravascular compartment thereby decreasing blood volume. This is compensated by a slow refilling from the interstitial space that depends on several tissue characteristics and is driven by hydrostatic and oncotic pressure gradients.[20] Plasma refilling counteracts the hypovolemia and prevents intradialytic complications. Whenever the ultrafiltration rate is higher than the refiling rate, the plasma volume declines and adverse manifestations can occur. These can be present as uncomfortable symptoms such as intradialytic hypotension, dizziness, cramps, nausea, vomiting, anxiety and syncope.[17]

Intradialytic symptoms may lead to premature dialysis cessation, need for saline, raise of dry weight, reduction in ultrafiltration rates and other interventions as a response to the distressing symptoms. They can also have an impact in life quality and may affect the trust and relation between the patient and the team, as well as compliance with dialysis therapy. The prescription of additional antihypertensive medication can appear as a solution but it makes the dry weight achievement further difficult. In addition, as described above, intradialytic hypotension is also related with poor outcomes.

Clinical assessment of dry weight can detect acute and important volume overload but is often insensitive to detect subtle variations and chronic overhydration. It is consequently imperative to maintain a high index of suspicion when relying exclusively on this method.

It is important to recollect that dry weight is not an immutable constant and should take in consideration many factors such as intercurrent illness, changes in body weight and composition, interdialytic weight gain and dialysis modality.

Nutrition and fluid intake play a role of paramount importance in the treatment of hemodialysis patients. These need to comply with a restrict diet with reduced sodium and fluid intake and the care providers may also need to implement a more efficient way of providing sodium removal with individualized adjustment of dialysate sodium concentration, modality and adequate treatment time.

Assimon et al.[21] concluded that when target weight is persistently not achieved there is an increased risk of emergency department visits and hospitalizations, reporting that >1.0 Kg above the prescribed target weight in more than 30% of hemodialysis sessions represented a higher absolute risk of hospitalization.

Dry weight reduction has been associated with significant reduction in blood pressure and LVH.[10] Attending to tolerability of symptoms, Sinha et al.[8] recommended that decrements as small as 0.2-0.3 kg per hemodialysis session could still be clinically significant and strengthen the patients trust.

Achieving and maintaining an adequate dry weigh is a continuous process that requires cautious attention and the effort of a multidisciplinary team.

5. Dry weight and fluid status assessment

Clinical assessment remains the basis for dry weight assessment worldwide and this includes a complete clinical history and physical examination. It is essential to look for excessive water and saline intake and explore the presence of interdialytic symptoms experienced by the patient (dyspnea, headache, postural dizziness). A complementory approach should include the evaluation of weight variations and blood pressure measurements with postural changes and examination of clinical signs of high blood pressure, edema and jugular turgescence,[18] percussion of abdomen and auscultation of the lungs. Clinical assessment remains essential but may not be enough to estimate volume overload since hemodialysis patients may frequently have an expanded ECW that is not enough to present edema.

A recent observational study with 39566 patients in 26 countries using a large dialysis network, has verified that fluid overload is a strong risk factor for death across different blood pressure categories and supported the need for a treatment policy that accounts for fluid status monitoring. The increased death risk related to fluid overload was even comparable with the risk associated with coronary artery disease, congestive heart failure or an age increase of ≥ 12 years.[22]

Wabel et al.[23] demonstrated that sometimes blood pressure is not well correlated with fluid status, therefore we should bare in mind that they are associated but not equivalent.

For these reasons other objective ways to quantify body water have been developed over the years:[24] biochemical markers like evaluation of N-terminal pro-B-natriuretic peptide (NT-proBNP); imaging markers as inferior vena cava (IVC) diameter and collapse index and lung water quantification using echocardiography; relative blood volume (RBV) monitoring and BIA (Table I). A brief revision of each one, supported by the current scientific evidence, will follow.

Table I. Comparison of dry weight and volume status evaluation methods

Technique	What is measured	Advantages	Limitations	Cardiovascular impact and mortality	References
Cardiac biomarkers	Blood sample: (a) ANP levels (b) BNP levels (c) Pro-BNP levels	Easy measurement Good relation with volume status (b) More sensitive than ANP (c) More sensitive than BNP	Invasive Influenced by underlying cardiac disease Widely variable	(b) and (c) Very sensitive and specific predictors of CV events in dialysis patients (b) Strong relationship to survival (c) Combination with other marker improves CV risk stratification for death and major CV events	25 26 27 28 29
IVC ultrasonography	IVC diameter IVC collapsibility	Noninvasive marker of intravascular volume and CVP	Operator dependent Affected by ventilation, right heart function and intra-abdominal and intra-thoracic pressures	Guided dry weight adjustment reported to be associated with LVH and prevention of cardiac chamber dilatation	30 31
Lung ultrasonography	Extracellular lung water B-line score	Noninvasive indirect marker of volume status and adequacy of estimated dry weight	Operator dependent Difficult to distinguish between interstitial edema of volume overload or other underlying disease No standardization	Degree of lung congestion reported to be an independent predictor of death and cardiovascular events	32 33
RBV	Light absorption Velocity of ultrasonographic waves	Noninvasive Real-time monitoring Prevention of intradialytic events	Does not give absolute blood volume, just relative % changes Influenced by ultrafiltration rate	Higher hospitalizations and mortality when RBV is used compared with controls RBV slopes were associated with all-cause mortality in long-term hemodialysis	20 34 35
Bioimpedance	Normalized resistance/resistivity of body compartments	Noninvasive Also allows nutritional status evaluation Numerical assessment of dry weight	Influenced by change in fluid distribution No standardization	Guided dry weight adjustment was associated with lower blood pressure and reduced arterial stiffness, but had little to no effect on all-cause mortality. Risk of overhydration determined by bioimpedance was associated with higher mortality	7 26 36 37

ANP, Atrial natriuretic peptide; BNP, Brain natriuretic peptide; CV, cardiovascular; CVP, Central venous pressure; IVC, Inferior vena cava; LVH, Left ventricle hypertrophy; NT-proBNP, N-terminal pro-B-natriuretic peptide; RBV, Relative blood volume.

5.1. Cardiac biomarkers measurement

Measurement of cardiac biomarkers was first introduced into clinical practice to diagnose heart failure but also revealed to be associated with renal insufficiency[38] and potentially useful in assessing volume status. The release of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) occurs as a physiological response to the distension and changes of pressure in heart chambers.[39] It therefore poses an estimative of blood volume.

BNP was proved to be a more specific marker to assess volume status and correlate strongly than ANP with volume overload and mortality.[40] NT-proBNP, an inactive fragment of BNP, was introduced into medical practice as having a longer half-life and was suggested to be superior to BNP in detecting cardiovascular events in hemodialysis patients.[25] Sheen et al.[41] concluded that BNP concentration varies during the course of the dialysis week reflecting correspondent volume changes. This however, does not correlate with weight or blood pressure variations.

Although these studies seem to show a strong association between cardiac biomarkers and overhydration, they lack specificity. It is therefore difficult to differentiate if natriuretic peptide level reflects true overhydration, underlying cardiac disease or a vascular leak secondary to inflammation.[28,29] It is also problematic to establish a “normal” range for dialysis patients, that allows clinical decisions, and studies have failed to establish its role in clinical practice.

A recent study aiming to investigate the role of NT-proBNP and galectin-3 in predicting death and cardiovascular events in asymptomatic hemodialysis patients, found that both biomarkers correlated with major outcomes, suggesting that their combined use may improve risk stratification and early therapeutic intervention.[27]

5.2. Inferior vena cava diameter and collapsibility

Central venous pressure (CVP) is related with intravascular volume, but its invasive nature (direct measure by catheter) makes it an unpractical method in daily practice. For this reason, ultrasound assessment of inferior vena cava diameter and collapsibility have been preferred as a noninvasive marker of intravascular volume and CVP.[30,42]

This technique was early suggested to be a reliable tool to estimate dry weight in hemodialysis patients.[43] When performing an echocardiographic examination of the IVC diameter and the calculation of its collapsibility with respiration, the detection of increased IVC diameter and decreased collapsibility suggests overhydration. Sekiguchi et al.[44] recently reported that IVC diameter and collapsibility accurately estimated CVP but did not predict intradialytic adverse events in hospitalized patients.

The ultrasound equipment can be easily accessed and the technique is innocuous and cheap. It however presents limitations: it may be difficult to perform by unexperienced physicians and in patients with large body habitus; show variability with ventilation, right heart function and intra-abdominal and intra-thoracic pressure[30].

Concerning the cardiovascular impact, IVC diameter measurement was suggested to be an excellent method to obtain ideal dry weight. Compared to control group, dry weight adjustment based on IVC diameter was reported to be associated with LVH reduction and prevention of cardiac chamber dilatation[31]. Regardless these encouraging results on cardiac pathological architectures changes, the study had a small sample size, making it insufficient to verify the utility of the technique.

5.3. Lung ultrasonography

Lung ultrasonography is a recent technique for volume status assessment. The method is based on sonographic findings termed “B-lines” that represent pulmonary interstitial edema and are related with fluid retention before treatment as well as its loss during dialysis. The findings are physiologically explained by the accumulation of water in the interstitium that makes the lung interlobular septa thicker, causing an ultrasound characteristic picture when the waves reach the interface between the water and the air of the lungs.[33] The detection and quantification of these hyper-echoic reflections may be helpful to evaluate dry weight of chronic hemodialysis patients, as well as the adequacy of fluid removal and the accuracy of dry weight estimated by usual clinical parameters.

A small study confirmed that the presence of pulmonary congestion can be useful to guide the dry weight determination. Even patients who had “clear" chest x-rays showed to have “B-lines” at lung ultrasonography, indicating pulmonary congestion and fluid overload.[32]

Liang et al.[45] also aimed to study the value of lung ultrasound in adjusting ultrafiltration volume and achieve dry weight. They performed ultrasound assessment of both extravascular water, by determination of B-line scores and pre-tibial skin tissue thickness, and intravascular water by determination of IVC diameter and left ventricle ejection fraction (LVEF). The parameters were correlated with ultrafiltration using pre and post-dialysis measurements. Among ultrasounds performed to quantify body water, ultrafiltration volume was only reported to correlate well with lung water reflected by B-line scores. All the scans were performed by an experienced radiologist. Patients with history of myocardial infarction, heart failure (abnormal LVEF) and active lung infection were excluded, which may bias the measurements.

This ultrasound technique is portable, non-invasive and can be performed by nephrologists after appropriate training. It remains unclear if removal of excessive pulmonary water leads to a state of true euvolemia and has impact in mortality and reduction of hospital admissions. Counting of B-lines score is not completely accurate, depending on the experience of the physician who is performing it and errors might occur. It is also difficult to differentiate between B-lines caused by interstitial edema and fibrosis and to distinguish if the edema is secondary to heart failure or pulmonary disease. In addition, this measurement may be inaccurate if performed in patients with obesity, history of emphysema, pneumectomy or pleurisy.[5]

There is insufficient data to estimate the value of assessing dry weight with lung ultrasonography and its impact on survival. The degree of lung congestion was however reported to be an independent predictor of death and cardiovascular events in hemodialysis population, better than the New York Heart Association (NYHA) score.[33]

5.4. Relative blood volume monitoring

RBV monitoring is another method proposed for dry weight estimation. It is assumed that there is no change in red cell mass and protein in the intravascular space during ultrafiltration, therefore the hematocrit and plasma protein concentration rise reflects a decrease in blood volume. During the dialysis session, the RBV decrease allows the estimation of volume status.

There are two different types of commercially available devices. One uses a photo-optical technology that continuously measures hematocrit through a chamber in the arterial end of the dialyzer and is attached to a monitor (Crit-Line monitor). The other measures the velocity of ultrasonographic waves travelling within the blood, which is dependent on total proteins concentration.

Sinha et al.[46] studied 150 hypertensive patients in order to validate the ability of this technique to assess dry weight, finding that patients who had their dry weight probed have steeper slopes that correlate with the magnitude of weight reduction. The authors concluded that patients with flatter slopes would be volume overloaded and this could predict the success of subsequent weight loss and blood pressure improvement. Most importantly, Agarwal et al.[35] reported that these slopes are related with all-cause mortality in long-term hemodialysis and may have prognostic value.

Other small studies suggest that RBV monitoring is a useful tool not only to stablish an adequate dry weight but also to reduce intradialytic morbidity.[47–49] RBV monitoring is defended to be a noninvasive, continuous, real-time monitoring of blood volume tool that may be helpful to reduce the incidence of intradialytic symptoms.

Despite these encouraging results, the use of RBV is still controversial. A significant large randomized study reported poorer outcomes when RBV is used.[34] The authors found higher hospitalizations and mortality when RBV is used compared with controls, though these results should be interpreted with caution due to their study design limitations.

5.5. Bioelectrical impedance analysis

BIA is a technique that allows not only the estimation of hydration status, but also lean tissue and fat mass. It is founded on the principle that, in biological tissues, higher frequency current passes through total body water (TBW), whereas lower frequency currents cannot bridge the cell membranes and travel preferentially in extracellular space.[50] The determined electrical resistance values and patient's gender, height and weight are used to extrapolate volumes, using validated equations.[51] It is used in different sophisticated versions and validations with different vector displays and frequencies (single/multiple frequency, segmental/total body measurements).

As a chronic disease, ESKD often leads to changes in body composition due to existence of multiple metabolic and nutritional disorders. BIA also allows nutritional assessment by detecting patients with higher risk of malnutrition and subsequent poor outcomes. When studying the nutritional status among the hemodialysis population, we find a combination of muscle wasting and tissue overhydration associated with aging, comorbidity and inflammation. Some studies using bioimpedance devices accounted for the nutrition status and calculation of lean tissue (mainly muscle) index as a predictor of mortality in hemodialysis, reporting significantly higher mortality when malnutrition and low lean tissue index are present.[7,52,53] In the general population, a higher body mass index is a well-known risk fact for cardiovascular disease but in hemodialysis patients it has a paradoxical protective effect being commonly associated with better outcomes.[54] This may be explained by the presence of multiple confounding factors (comorbidities, chronic inflammation and metabolic acidosis) that result in body energy waste. For these reasons, a cautious nutritional evaluation is of paramount value in hemodialysis patients and BIA is a noteworthy tool that may be used for this purpose.

Several studies were performed to investigate the influence of BIA fluid management on cardiovascular health and patient survival. These used different approaches in interpreting data derived from BIA to determine the hydration status (ECW/TBW ratio, ECW volume, overhydration index).

Wizemann et al.[7] proposed the cut-off point of 15% for a relative hydration status, which represented an ECW excess of approximately 2.5L, showing that mortality significantly increases above this level. Later, Onofriescu et al.[55] described a new cut-off point of 17.4% for relative fluid overload that would better predict mortality risk. Other investigators have proposed that a derived BIA parameter, time averaged fluid overload (TAFO), would better reflect the long-term cardiovascular fluid load.[56] Hecking et al.[57] defends that the best fluid marker for dry weight determination is fluid overload measured post-dialysis and it should be recommended for clinical practice.

Several studies have been consistent with the conviction that a bioimpedance guided optimization of volume status may improve outcomes, but a recent systematic review and meta-analysis including only randomized controlled trials, goes against these findings. Covic et al.[36] intended to analyse the benefits and harms of BIA to guide fluid overload and its effect on all-cause mortality, concluding that BIA-based dry weight assessment was associated with lower blood pressure and reduced arterial stiffness, but correction of overhydration had little to no effect on all-cause mortality. The authors suggest these negative findings to be interpreted with caution, since size and power of the included studies was low.

Another systematic review and meta-analysis, published a few months later, aiming to evaluate the risk of overhydration and low lean tissue index using a body composition monitor, concluded that both were associated with higher mortality.[37]

Another study using BIA was also consistent proving the importance of fluid status control and mortality risk, but unexpectedly concluded that low interdialytic weight gain (IDWG) was also related with mortality, which is suggestive of protein-energy wasting, inflammation and malnutrition. The two distinct measurements seem to have prognostic impact in hemodialysis patients and both can be obtained by BIA.[57]

Davies et al.[26] suggested that BIA could not distinguish between plasma volume and volume in the extravascular compartment, leading to progressive tissue overhydration in patients with muscle wasting. They also alerted to the risk of residual kidney function loss and suggested the combination of BIA with measurement of cardiac biomarkers, minimizing the risks in the optimization of a target weight.

BIA is a noninvasive, fast, reproducible and an easy to perform technique. In addition, it is the only method that allows a numerical assessment of dry weight and determination of both overhydration and volume depletion. It also has several limitations: it cannot be performed in patients with an implanted electronic medical device, connected to an external medical device or with any kind of metal implants or prosthetic joints, major amputations, symptomatic aortic valve stenosis and in pregnant women. It can also be unreliable in the presence of cardiac insufficiency, which is a prevalent comorbidity of hemodialysis patients.

5.6. Combined **approach for dry weight assessment**

Virtually all trials addressing dry weight assessment combine an initial clinical approach with an instrumental method. This highlights that the cornerstone for guidance is still clinical.

Few studies used approaches without some degree of clinical assessment in both comparisons. A randomized controlled trial[58] showed that a protocol associating lung ultrasonography and BIA guided dry weight adjustment, as compared to clinical evaluation, does not reduce all-cause mortality and/or cardiovascular events in hemodialysis patients with a low cardiovascular risk. This was the only randomized trial that studied lung ultrasonography for treatment guidance and also concluded that this technique is less sensitive, though more specific than BIA.

Different techniques may also be combined in order to assess volume and monitor complications. In a recent randomized controlled trial, Antlanger et al.[59] included hemodialysis patients with overhydration determined by BIA and studied the effect of dry weight reduction and the occurrence of complications. The primary outcome, intra and post-dialytic adverse events, was evaluated based on blood volume-monitored regulation of ultrafiltration. The authors highlighted the high incidence of intradialytic morbidity and discourage rapid volume corrections.

6. Discussion

The concept of dry weight and its determination is firmly related with detection of volume overload. This is one of the key causes of cardiovascular events and death in hemodialysis patients and is also accountable for morbidity and hospitalizations. Hence, volume overload is also undoubtedly costly, being reported that among United States hemodialysis patients, total costs derived from poor control were approximately $266 million during a 2 years follow-up period.[60] Its effects are cumulative and there is a significant component of death risk that could be improved by using accurate techniques and protocols.

Both clinical and instrumental techniques have been discussed and investigated to guide fluid management and dry weight determination in order to improve cardiovascular outcomes. The topic is important but the results are conflicting in observational and randomized controlled trials. We should carefully scrutinise the results and consider its limitations to understand the barriers for dry weight determination.

Besides the obvious difficulties in the assessment of volume status and true dry weigh, other problems have also been identified. Reduction of post-hemodialysis body weight is difficult due to the development of intradialytic hypotension, which is closely related with high ultrafiltration rate. In addition, higher ultrafiltration rates are also associated with higher mortality.[61] In order to achieve a reduction without causing symptoms, possible solutions are to increase frequency and/or duration of hemodialysis sessions[62] and reduce IDWG. Increasing duration and frequency is financially and logistically difficult to implement and could affect patient compliance and quality of life. This makes that dietary salt and water intake, key factors for the IDWG, should be the crucial determinants for optimizing volume control in hemodialysis patients. High dietary sodium intake is already reported to be independently associated with higher mortality in a dose dependent manner.[63] We should limit IDWG but always keep in mind that low IDWG and energy waist are also related with mortality.[57]

The non compliant patient is perhaps the most important barrier for success. Diet compliance can contribute to the variability of results and is a modifiable factor that can be improved with counselling. Lifestyle modifications are not easy to implement in this population and harder to maintain over the years. We should find and work on strategies to improve compliance and obtain constructive results. Some studies suggest that individual cognitive behavioural therapy leads to improvements in life quality, compliance and depression, which is very prevalent in these patients.[64,65] The dialysis care provider should be aware of the role played by extracellular fluid overload and the importance of diet compliance to be motivated to act.

Clinical evaluation is still the cornerstone of dry weight assessment but combination and cross validation of different techniques may be the future optimal solution. The most promising method seems to be BIA and its use is already widespread. There is still the need for more evidence to stablish the best marker and cut-off for derived volumes. It is currently to be proved which is the most intuitive and best suited marker to guide fluid management and improve the cardiovascular outcome. Clinical trials suffer from other important limitations associated with study design, randomization and performance bias. Some had no control group or randomization between groups,[9,56] other had a design with a cross-sectional assessment of hydration status only at the beginning of the study,[7] or an intensive fluid status optimization[56] unfeasible in real life long-term follow-up of dialysis patients. Also, different clinical endpoints associated with hypervolemia such as blood pressure, left ventricular mass and arterial stiffness were inconsistently used.

Two different systematic reviews and meta-analysis evaluating bioimpedance assessment of volume overload and mortality showed conflicting results. Their inclusion criteria was different and this may be due to the fact that there is no standard cut-off/marker to consider if a patient is volume overloaded. Hwang et al.[37] included only studies with hemodialysis patients and identified overhydration based on fluid excess ≥ 15%. Both intervention and control groups were evaluated using a BIA device with no attempt to correct overhydration. Covic et al.[36] systematic review and meta-analysis included a small number of patients of both hemodialysis and peritoneal dialysis. They included studies that used various manners of reporting the outcomes and different parameters to identify the patient as overhydrated. The control group had a clinical-based prescription of dry weight and the intervention group was assessed by BIA in order to adjust target dry weight based on the obtained results.

An important advantage of BIA is that is the only method that allows a numerical determination of the optimally estimated dry weight. Ecographyc methods depend on the operator experience and approach, which may bias measurements and maximize errors. Implementation of ultrasound techniques is also difficult since they require trained physicians to minimize errors and variability, which is logistically difficult to provide. Muniz et al.[66] compared results of IVC ultrasound evaluation performed by nephrologists and cardiologists and found a strong correlation between both, but these results may not be reproducible.

It is necessary to highlight the importance of hemodynamic tolerability of treatment sessions in order to prevent cardiovascular damage and subsequent morbidity caused by end-organ hypoperfusion. Decrements of target weight should not be aggressive, otherwise they may trigger a continuous vicious cycle of volume depletion and interdialytic weight gains.

A precise estimation of pre-dialysis fluid status may theoretically help in preventing short and long-term cardiovascular complications. Nonetheless, when leaning towards one goal, we might be decompensating and causing stress in one other. We should have an integrative view of the patient and ESKD as a chronic disease and a condition of multiple insults. Complementary diagnostic techniques may be a powerful tool for identifying patients with high risk of adverse outcomes and protecting them against harmful effects of both volume overload and depletion.

Studies have focussed in controlling volume, weight and blood pressure, attending to symptoms and cardiovascular disease, but few have given value to potential risks as preservation of residual kidney function. Faster rates of residual kidney function loss are associated with mortality, worse life quality, occurrence of hypotensive episodes and cardiac stunning.[67,68] An interesting multicentre randomized trial is ongoing in order to determine if BIA guided fluid management can reduce the deterioration of residual kidney function and improve clinical outcomes by preventing fluid depletion.[68]

Heterogeneous findings in the different techniques are not surprising and require more investigation before their routine use can be implemented, since no single positive or negative study should be interpreted as definitive evidence.

7. Conclusion

We should consider the benefits and harms of probing dry weight in qualified large long-term randomized trials, as well as continue testing potential effectiveness of accurate clinical evaluation and/or instrumental techniques. Further studies should be designed to ensure compliance with a prescribed diet and the control group should always use a realistic and feasible clinical evaluation to assure beneficial outcomes. The ideal method should be accessible, noninvasive and easy to perform. Risks associated with dry weight achievement are bidirectional, implying that both volume overload and depletion may represent a threat to patients. Avoiding aggressive dry weight management and promoting tolerability of symptoms and hemodynamic stability should be a priority.

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