Fluid Overload for Protein Energy Malnutrition

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Protein energy malnutrition is recognized as a leading cause of morbidity and mortality in dialysis patients. Protein–energy-wasting process is observed in about 45% of the dialysis population using common biomarkers worldwide. Although several factors are implicated in protein energy wasting, inflammation and oxidative stress mechanisms play a central role in this pathogenic process. Fluid overload and fluid depletion mimic a tide up and down phenomenon that contributes to inducing hypercatabolism and stimulates oxidation phosphorylation mechanisms at the cellular level in particular muscles. This endogenous metabolic water production may contribute to hyponatremia. In addition, salt tissue accumulation likely contributes to hypercatabolic state through locally inflammatory and immune-mediated mechanisms but also contributes to the perturbation of hormone receptors.

sodium water fluid overload fluid depletion

1. Introduction

Malnutrition is a common disorder in dialysis patients [1][2][3]. Protein–energy malnutrition (PEM) or protein–energy-wasting (PEW) process is the most commonly observed manifestation of this disorder [4]. As stated, in PEW process, malnutrition affects the two main components of body composition, namely protein stores (muscle mass, sarcopenia) and energy stores (fat mass) with different behaviors and/or severities [5]. According to recent reviews, the prevalence of PEM in dialysis patients may range between 15 and 75% [6]. This imprecise estimate reflects several factors that are poorly considered, such as criteria used to define PEM, variability of existing assessment tools, age-related factors, geographical differences, stages of chronic kidney disease, and effects of renal replacement modalities [4][7][8][9]. Chronic kidney disease progression is associated with a worsening of protein energy malnutrition, culminating in end-stage kidney disease and in dialysis patients [10]. This deleterious phenomenon has been clearly highlighted within the MDRD study and directly linked to the aggravation of uremic disorders marked by a spontaneous reduction of diet caloric and protein intakes [11][12]. In a recent international systematic review by Carrero et al., it was shown that prevalence of PEM in dialysis patients averaged 45% worldwide but with large variations according to country incomes [6]. As clearly identified here, prevalence of PEM was 39%, 48%, and 63% in high-, middle-, and low-income countries, respectively [6].

Protein–energy malnutrition in dialysis patients is most often characterized by inflammation and oxidative stress mechanisms [13][14][15][16][17][18]. Inflammation was identified early by researchers of Karolinska's group as a prominent and common marker of malnutrition and atherosclerosis process in dialysis patients, the so-called malnutrition inflammation atherosclerosis (MIA) syndrome [19][20]. Later on, subclinical chronic inflammation was

confirmed by independent researchers as being associated in a broader pathophysiologic spectrum called malnutrition inflammation complex syndrome (MICS) [13][14].

2. Fluid Overload as a Cause of Protein Energy Malnutrition: Evidence-Based Facts

In this context, sodium and fluid imbalance, as well as their management, are emerging factors that contribute to protein–energy malnutrition. This is the main focus to highlight this overlooked problem in dialysis patients. To facilitate description of the link between fluid disorders and protein energy malnutrition, researchers split this pathway into two parts, fitting with tides phenomena of intermittent hemodialysis. In brief, the tides up phenomenon reflects fluid and sodium accumulation occurring during the interdialytic period (as a result of diet and fluid intake and residual diuresis), while the tides down phenomenon reflects fluid and sodium depletion resulting from dialytic treatment (as a result of ultrafiltration and sodium depletion). Interestingly, both conditions are associated with the protein–energy-wasting process.

Chronic fluid overload (FO), a surrogate marker of water bound sodium excess, is quite common in hemodialysis patients. According to the method used to assess fluid status in dialysis patients (clinical, instrumental, biomarkers), FO prevalence may differ substantially. Using a non-invasive objective tool, such as multifrequency bioimpedance, to estimate fluid status, it was determined that FO is present in 40 to 60% of dialysis patients. In this context, it is interesting to note that FO prevalence is almost similar in hemodialysis and peritoneal dialysis patients, as shown in recent prospective international studies using the same MF-BIA tool [21][22][23][24]. Large retrospective cohort studies (MONDO Initiative) assessing FO with MF-BIA have consistently reported a higher mortality risk associated with FO in prevalent HD patients [25][26][27][28]. Furthermore, in these studies, it was also shown that the relative risk of death was positively associated with fluid overload degree independently from blood pressure levels and strongly linked to malnutrition inflammation complex syndrome [13][26][27][29]. These findings have been confirmed in a large international cohort study involving incident HD patients. As shown in this entry, fluid overload at baseline is associated with 30% higher mortality risk at 12 months, increasing to 60% when FO was present one year later. Interestingly, mortality mainly from cardiovascular origins was associated with the degree of FO independently from blood pressure levels and worsened with higher time exposure [23]. These findings indicate that fluid overload is a common feature in dialysis patients, frequently associated with hypoalbuminemia, protein energy wasting process, and inflammatory markers, that highlights an unmet medical need [30].

Tissue sodium accumulation, as a surrogate marker of water free sodium stored in skin and muscle, is another common feature of kidney disease and dialysis patients recently identified as an additional vital risk factor [31]. Tissue sodium content, as measured via 23 Na MRI, is substantially increased in kidney disease and dialysis patients, with additional conditions that tend to worsen this condition (i.e., ageing, hypertension, cardiac, diabetes, salt diet, dialysate sodium) [32][33][34][35]. It is also shown in experimental and clinical studies that tissue sodium accumulation contributes via insulin resistance and inflammation to protein–energy wasting [33][36][37].

Hyponatremia, a well-known marker of poor outcome in hemodialysis patients [38] has been recently associated with severe fluid mixed disorders linked to intercurrent illnesses [25][26][39][40]. Additionally, it has been shown in a large Japanese study that patients' outcomes (all-cause mortality, stroke, lower limb amputation) were worsened with positive plasma sodium changes and improved by negative plasma sodium changes [41]. These findings suggest that increasing fluid volume depletion in isotonic (isonatric) or hypotonic (hyponatric) dialysis conditions is preferable for improving outcome. As shown in a recent study monitoring natremia in hemodialysis patients using an automated sensor device, hypotonic hyponatremia was detected in about 10% of patients and in all cases was associated with a protein–energy-wasting and inflammatory process due to severe intercurrent illness [42]. Interestingly, correction of illness and readjustment of fluid status by significant reduction of dry weight up to 20% with isonatric dialysis were able in the majority of cases to mitigate risk, to correct hyponatremia, and to improve patients' outcomes.

Clinical evidence linking fluid imbalance in dialysis patients with poor outcomes has been briefly summarized in this paragraph. Interestingly, all pathophysiologic pathways involved in these deleterious mechanisms are mediated by inflammation and associated with the protein–energy-wasting process [25].

3. Pathophysiologic Mechanisms Linking Fluid Overload, Fluid Management, and Protein Energy Malnutrition

While FO, inflammation, and malnutrition are independent risk factors for mortality [20][26][27][41], recent studies have shown that their combined presence may lead to a cumulative risk profile [23][43]. From a pathophysiologic perspective, FO, inflammation, and protein energy malnutrition can also be mutually reinforcing and can act both ways—from FO to inflammation and vice versa—suggesting that inflammation axis is the main cause of malnutrition [25]. Clinical evidence linking FO and inflammation has been recently summarized in a narrative review using objective tools to assess fluid status (multifrequency bioimpedance, cardiac biomarkers) and inflammation biomarkers (CRP, IL6) [30]. The pathophysiologic link is not clearly understood but likely involves several mechanisms: endothelial dysfunction and increased vascular cell adhesion molecules (VCAM-1); vascular leakage (increased capillary leak, angiopoietin 2); hypoalbuminemia resulting from reorientation of liver protein synthesis to acute phase proteins in case of inflammation [44][45]; muscle proteolysis due to reprioritization of cellular energy metabolism facing sodium accumulation or acute depletion [46][47]; gut endotoxin translocation (congestion or ischemia) [48]; pulmonary alveolar edema (breakdown of alveolar epithelial barrier) [49][50]; and finally tissue sodium storage activating immune and inflammatory pathways (water-free sodium, lymphocytes Th-17) [51][52][53].

Rapid sodium removal and fluid depletion as summarized by high ultrafiltration rate (>10 mL/h/kg) may lead to poor outcomes with increased cardiac risks [54][55]. This has been consistently shown in several studies suggesting that intensive or aggressive fluid management may lead to unwanted side effects. While these dialysis-induced risks are mainly mediated using hypovolemia and repetitive ischemic cardiac insults [46][56], some recent findings in animal experimental models suggest that fast sodium removal may trigger catabolism, with reprioritization of cell metabolism being associated with muscle proteolysis (release of free amino acids) to maintain tissue sodium content [47][57][58]. Fast sodium removal achieved through hemodialysis via ultrafiltration and negative dialysate–

plasma sodium gradient is likely to contribute to muscle proteolysis and dialysis-induced protein catabolism [59][60][61]. In addition, as recently shown in a phosphate kinetic study relying on magnetic resonance spectroscopy, hemodialysis tends to preferentially deplete phosphate from the intracellular compartment, reducing the availability of high-energy phosphates and impairing ultimately mitochondrion and cellular metabolism [62].

Tissue sodium accumulation (skin, muscle) is associated with various pathophysiologic findings involving on one side the cardiovascular system (i.e., hypertension, left ventricular hypertrophy) independently from pressure level and mechanical consequences but on the other side various metabolic pathways that have direct effects on nutritional status (i.e., insulin resistance, muscle catabolism, cell energy metabolism) [31][33][63]. To reconcile the mismatch, the authors advocated surplus endogenous free water generation from exaggerated catabolic reactions and from enhanced renal accrual, which would make any extra exogenous water intake unnecessary [57][58].

Hyponatremia is difficult to explain in an anuric dialysis patient in which dialysis is the main source of exchange (sodium and water) with external milieu [38]. Several hypotheses have been advocated: Firstly, the release of mediators (vasopressin, angiotensin 2) [64] or factors (tonicity, thirst) that affect sodium-free water intake or retention; secondly, vascular leakage and sick-cell syndrome linked to inflammation that facilitate water intercompartmental imbalance [65][66]; thirdly, reorientation of liver protein synthesis to acute phase proteins, reducing albumin circulating levels. A new and interesting hypothesis may be formulated according to the findings in rodent models of tissue sodium content on muscle metabolism. As suggested by this model, muscle catabolism and renal recycling of urea in presence of tissue salt excess was found to be a key osmotic force in minimizing free water loss [47]. In the context of dialysis patients, tissue salt accumulation and depletion might be perceived as the main driving forces of tissue catabolism (proteins, carbohydrates, lipids) and oxidation mechanisms leading to increased endogenous production of metabolic water (sodium-free) [67]. In this case, hyponatremia will result from a salt-driven catabolic state, with muscle mass loss, enhanced proteins, carbohydrate and lipid breakdown, as well as from reprioritization of global energy muscle metabolism at the cellular level (mitochondrion) associated with an intense oxidation phosphorylation process leading to an excessive production and accumulation of endogenous metabolic water (sodium-free) [67].

In brief, these tides up and down phenomena, reflecting interdialytic fluid and sodium accumulation and intradialytic fluid and sodium depletion, respectively, are likely involved in the protein–energy malnutrition of hemodialysis patients [63]. During a tide up phenomenon, sodium and fluid accumulation tends to trigger inflammation and its related consequences (inflammation axis). During a tide down phenomenon, sodium and fluid depletion associated with stressors of dialysis-induced systemic stress tend to trigger catabolism and muscle proteolysis.

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