Volume Overload in CKD

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Introduction

Fluid balance

is generally defined by the difference between the daily fluid input and the daily fluid output and it should not be associated with weight and insensible losses, but it could be correlated with dialysis fluid removal if an individual is on renal replacement therapy

'Fluid overload' (FO)

- is defined by a percentage of body weight – a cut-off value of 10 % has been associated with increased mortality
- Volume overload (VO) is a common scene for patients on RRT but, also for those with pre-dialysis chronic kidney disease (CKD), even though only a limited number of studies have been conducted in these patients

All studies performed *until now in CKD patients described a significant proportion of overhydrated patients, even in the absence of clinically detectable signs of hypervolemia*

Chronic VO leads to hypertension

left ventricular hyper-trophy (LVH)

increased arterial stiffness

heart failure (HF),

and even an increased morbidity and mortality, especially in dialysis patients

- several studies shown
- VO is considered to be an important contributor to an adverse prognosis, an effect modifier and an independent predictor of all-cause and cardiovascular (CV) mortality in
- pre-dialysis CKD patients and end stage renal disease (ESRD) patients on RRT

One of those study :

Tsai et al. reported, in 472 non- dialysis patients with stage 4–5 CKD, a significant statistical association between the severity of VO and an increased risk of rapid decline in

renal function and necessity of RRT initiation

VO was found to be a better predictor of renal dysfunction progression than the presence

of diabetes (DM) in these patients

Also, in non-renal clinical settings, VO is the primary cause of hospital admission and readmission of patients with HF and it is with associated with HF progression

Sodium and Water Metabolism: The Importance of the Kidney

- Pathophysiology
- oldest theory of VO:
- Tonicity is characterized by the movement of the osmoles on the interior and exterior of a cell causing, therefore, the movement of water.
- The body fluids tonicity is maintained within normal range (280 mOsm) throughout homeostatic mechanisms that supervise the intake and excretion of water and sodium (Na)

Important for these processes are:

- the function of thirst and the secretion of the antidiuretic hormone (ADH), by activation of hypothalamic osmoreceptors in response to changes in tonicity;

- the kidney – participating in the maintenance of normal water and Na balance, as it both preserves and removes water and Na (Na reabsorption, vasopressin release, the medullary gradient)

it is important to differentiate the mechanisms that control water balance (tonicity, osmoregulation) from the mechanisms that control Na balance (extracellular volume).

Anomalies of water balance determine modifications of serum Na concentration, leading to hypo/hypernatremia,

whereas anomalies of sodium balance determine modifications of the extracellular volume (ECV), leading to volume depletion/volume overload.

- Water balance is primarily controlled by thirst and the ability of the kidney to produce more concentrated urine when osmolality increases or more diluted urine when osmo-lality decreases
- The most important inductor of thirst is hypertonicity, with a sensitivity of only 2–3 % increase in the plasma osmolality.

- In normal individuals, the osmotic threshold of thirst is approximately 290–295 mOsm/kg H_2O
- ADH secretion is stimulated primarily by hyper-osmolality and by arterial volume decrease (HF, cirrhosis, vomiting)
- The osmotic threshold for ADH release is 288–290 mOsm/kg

- if ADH levels are very high (like in chronic HF), water channel remains permanently in the plasma membrane leading to continuous water reabsorption, leading to interstitial water excess and edema

New Insights on the Pathophysiology of Volume Overload

Role of Interstitial Fluid Compartment in Fluid Homeostasis

- Recently, an essential role of the interstitium in the underlying mechanisms involved in fluid homeostasis was recognized
- Interstitial fluid pressure is determined by a complex interplay between the fluid influx (blood capillary filtration), the fluid outflow (lymph flow), and the compartment's ability to expand (tissue compliance)

- The interstitial fluid pressures are negative in healthy subjects and positive in CKD patients, but with no association between body fluid volumes and blood pressure
- Moreover, it seems that the increase in the interstitial fluid pressure observed in CKD compensatory changes in the local microcirculation and this could further lead to either reduced trans capillary filtration in the interstitial , or to an increased lymph flow

- Acute interstitial VO is associated with relatively quick boosts of interstitial fluid pressures, while interstitial fluid excess in chronic edematous state cause only moderate escalation of interstitial fluid pressure

- relative fluid shift from the interstitial into the intravascular space is induced by a high sodium intake.
- In the Heer et al.'s study 50–550 mmol of Na were given to normal men in order to sodium balance evaluate
- Plasma volume increased by about 330 ml when Na intake was 550 mmol/ day, but without modifcations of TBW or body weight even
- when Na intake was as high as 1,700 mmol.

- It is noticed that Na storage does not determine body weight modifications

- Another important cohort study enrolled hypertensive patients and normotensive control subjects and showed that patients with refractory hypertension had increased tissue Na content, assessed by Na-MRI measurements, in comparison to control subjects

Cardiotonic Steroids (CTS): Involvement in CKD

- CTS are also called 'digoxin-like' endogenous substances found in the serum and urine of uremic and overhydrated patients and, also, in other clinic conditions, such CHF ,hypertension, renal ischemia and preeclampsia

- They represent a relatively new discovered
  class of endogenous cardio tonic steroid hormones that act as a specific ligand for the Na/K-ATPase Tran membrane protein on
  the surface of cardiomyocytes

It has previously been reported that marinobufagenin (MBG), an endogenous bufadiendolide CTS, is elevated in both in clinical and experimental renal failure

(MBG), has a greater importance in the pathogenesis of renal failure

It appears, therefore, that CTS and especially MBG might become the new therapeutic targets in the management of uremic

Cardiomyopathy and over load diseases

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Haller et al. found that in experimental chronic renal failure, increased levels of MBG contribute to hypertension and cardiac fibrosis through suppression of this transcription factor and suggested that this could represent a new potential therapeutic target

Malnutrition-Inflammation and VO in CKD

- Protein-energy malnutrition (PEM) develops when the diet cannot satisfy the body's need for protein and/or energy – a frequent status in dialysis patients
- PEM is accountable for a poor quality of life and increased all-cause mortality in ESRD patients [

- In renal patients, there is an important pro-inflammatory status
- Inflammation promotes atherosclerosis ,
- The term of malnutrition-inflammation-atherosclerosis' (MIA) syndrome or 'malnutrition- inflammation complex syndrome'
- (MICS) has been adopted. MIA syndrome is considered as one of the main cause of mortality in ESRD patients

- New recent studies are associating to a greater degree malnutrition and inflammation with VO
- Hung et al. found in 338 pre dialysis CKD patients the volume overload was positively correlated with IL-6 and TNFa and the only parameter that was strongly associated with all components of the MICS syndrome.
- At the same time, the presence of MICS had additive deleterious effects to VO.

- Lately, endotoxemia appears to become a new piece in the puzzle of systemic inflammation of renal patients with VO.

Assessment of Fluid Status in CKD

- One of the most important tasks for a nephrologist is the correct assessment of fluid status.
- ESRD patients, treated by a standard dialysis prescription, are affected by chronic volume overload and by intermittent inter dialyitic weight gain (IDWG).
- Statistical analyses demonstrate an association between these two conditions and mortality

- An inaccurate assessment of dry weight leads to hypertension/hypotension, cardiac and vascular dysfunction, omission of small changes in nutritional status, and intradialytic morbidity and mortality

Clinical Assessment of Fluid Status in Chronic Kidney Disease

- This was the first method used for the estimation of a patient's water status, but its use as a unique assessment tool has been plagued by its lack of sensibility and specificity.
- It comprises the evaluation of: BP, pedal edema, pulmonary congestion rales, turgid jugular veins, dyspnea, weight increase, history of previously excessive salt and water intake and the maximum ultrafiltration tolerated by the patient

There are several important shortcomings:

- a patient can present ECV excess without displaying signs/symptoms of VO
- high BP levels are not a reliable tool for assessment of VO as there is a proportion of patients that are normotensive despite VO and other patients that are hypertensive but normovolemic.

- pedal edema cannot account only for VO, being, also, present in cases of vascular stasis, use of calcium channel blockers or venous insufficiency; in contrast,
- a large proportion of volume overloaded patients does not present edema

- weight changes can occur, also due to nutritional diet modifications or poor nutritional status and cannot be judge only on ECV variations
- clinical evaluation remains an important
- fluid status assessment tool in the hands of well-trained, experienced nephrologists.

Echocardiography and Inferior Vena Cava Measurements

In early CKD stages, LVH develops as a physiological response to pressure and VO, but its prevalence and severity increases with progressive loss of renal function leading to structural changes due to chronic overload and CKD-associated factors.

In dialysis

patients, LV volumes fluctuates due to chronic VO, and the presence of associated cardiac impairment, so, echocardiography

should be performed at an achieved DW, for reliable results

- Measurement of IVC is a simple, rapid and non-invasive method of fluid status assessment

- In dialysis patients, LV volumes fluctuates due to chronic VO
- A 2010 study, performed in 160 HD patients, could not correlate VO with an IVC augmentation, measured before the midweek HD session, and concluded that IVC has a positive predictive value of VO of only 18 %, with an important proportion of false negative cases (45 %)

Biomarkers of Volume Overload in CKD

In CKD patients, BNPB-type natriuretic peptide (BNP) and NT proBNP were correlated with renal function decline

Bioimpedance Analysis (BIA) in CKD

This represents a non-invasive, volume measurement technique based on the electrical principle that the body is a circuit with a given resistance (opposition of high and low frequency current flow between intracellular and extracellular compartments) and a given reactance (the ability of cells to store energy)

- BIA is a useful tool for fluid management in pre-dialysis CKD patients. There are several studies that are suggesting the importance of BIA in these patients for a better estimation of over hydration and improvement in clinical management

Blood Volume Monitoring (BVM) and Volume Overload

This technique uses relative blood volume (RBV) monitoring devices incorporated in the dialysis machine that allow non-invasive, real-time assessment of intra-dialysis changes of hemoglobin/hematocrit concentrations (by optical absorbance) or of the concentration of total plasma protein (by ultrasound recorded blood waves velocities)

- The BVM method has been proposed for predicting DW but was, initially, conceived for a better management of intra-dialysis hypotension

Heart Rate Variability (HRV) and Volume Overload in CKD

- HRV is a simple, non-invasive technique used to evaluate cardiac dysautonomy in healthy individuals as well as in pathological settings
- The HRV measurement provides data about the sympathetic and parasympathetic activity and reflects the ability of the sinoatrial node to modify the heart rate
- In a simple manner, it measures the periodic variations in R-R interval from beat to beat

VO and CKD Progression

- Tsai et al. published in 2014 the results of a prospective cohort study
- The study showed that VO was independently associated with an increased risk of rapid GFR decline and that the severity of VO was associated with an increased risk of RRT initiation

Volume Overload Treatment: Sodium Plays the 'Leading Role

Pre-dialysis CKD Patients

In pre-dialysis CKD patients, excess Na intake – as a risk factor determines VO increased BP and proteinuria.

Therefore, controlling salt intake could account for a simple, modifi able measure for reduction of VO, BP and proteinuria,

the principal conditions leading to CKD progression

- Reports show that 80–89 % of CKD patients ingest
- >100 mmol Na/day, a higher amount than
- what the guidelines are recommending

Renal Replacement Therapy Patients

- Volume control and sodium restriction is associated with improved BP values and increased survival rates in dialysis patients.
- lower Na intake leads to a reduction in BP and LVH and higher Na levels are associated with both elevated BP and IDWG

A number of proposed strategies were created over time for a better control of fluid status and BP: (1) Na profiling (modeling);

(2) Na individualization;

(3) UF profiling;

(4) different HD techniques

VO and Survival

Poor volume control is

mainly related to at least three factors

(i) weight gain (IDWG);

(ii) high ultrafiltration rate (UFR)

causing as a consequence hypotension and (

iii) chronic volume over load.

high inter dialytic

- Comorbidities and lower dialysis dose were also associated with higher mortality risk
- High UFR could induce hemodynamics instability, intradialytic hypotension (IDH) and increased mortality risk
- Hypotension during HD and aggressive UFR increase the risk for intra dialytic recurrent myocardial stunning and could determine, over time, irreversible fibrotic changes and chronic heart failure, arrhythmias and sudden cardiac death

Summary

- Progressive loss of renal function causes reduced sodium filtration and inappropriate suppression of tubular reabsorption that ultimately lead to volume expansion
- Fluid overload frequently manifests in patients with moderate to particularly late stages of CKD and has been associated with hypertension, congestive heart failure (CHF), left ventricular hypertrophy (LVH) as well as
- Edema
- Volume overload is related to CVD3,4 and is a predictor of outcome in hemodialysis and peritoneal dialysis.

Thank you