Perspective

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Hemoadsorption Combined with Hemodialysis and the "Inflammation Mitigation Hypothesis"

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ABSTRACT

Clinical outcomes are still unsatisfactory in patients undergoing chronic maintenance dialysis. Signs and symptoms of uremic intoxication are often present even in presence of an adequate dialysis delivery. These along with cardiovascular and skeletal complications, have been correlated to the accumulation of inflammatory chemical mediators, beta-2 microglobulin (β2M), parathyroid hormone (PTH) and other middle to large molecular weight toxins that are insufficiently cleared by current dialysis techniques. Such condition determines a vicious loop where a subclinical status of inflammation causes a disruption of the immunological response affecting outcomes by accelerated atherosclerosis, anemia, and frequent infections. The overall picture can be described as a systemic inflammatory syndrome with simultaneous activation of the innate and the adaptive immunity. In such condition, new options and techniques are required to achieve a more effective blood purification and to correct the altered immuno-homeostasis. New efficient and biocompatible sorbents are today available (HA 130 Cartridge, Jafron Medical, Zhuhai, China) and they can be advantageously coupled in series with the hemodialyzer to perform hemoadsorption combined with hemodialysis (HA-HD). This technique has been already studied in at least two randomized trials demonstrating an effective improvement of clinical and biochemical outcomes. We have calculated the kinetics of β2M in a single session, in a series of three consecutive sessions of a week and in a period of three months using different frequencies of application (first month: Three sessions per week; second month: Two sessions per week; third month: One session per week). In the single session the reduction ratio was superior to other techniques such as hemodialysis (HD), high-flux hemodialysis (HFD) or hemodiafiltration (HDF). In the thrice weekly regime, the time average concentration (TAC) of β2M resulted inferior to HD and HDF. In the long period, a lower concentration of β2M was maintained even with a once-a-week regime. Considering the parallel reduction of inflammatory parameters, we could hypothesize that the enhanced removal of uremic toxins and chemical mediators led to a mitigation of the systemic inflammation with a progressive reduction in the generation of β2M. This "inflammation mitigation hypothesis (IMH)" supports the prescription of HA-HD once a week, possibly after a month of thrice weekly regime.

Key words: Hemoadsorption, sorbents, hemodialysis, inflammation, uremia, cytokines

INTRODUCTION

In the setting of intensive care, patients with sepsis or acute kidney injury (AKI) often present a clinical picture of dysregulated immunological response syndrome.[1–3] When this response is uncontrolled, a typical cytokine release syndrome (CRS) may occur, and patients experience endothelial dysfunction, hemodynamic instability and multiple organ failure. CRS can be caused by bacteria, virus or other stimuli that induce a significant activation of innate and adaptive immunity and, consequently, an uncontrolled inflammatory response.[4–7] This picture is common in sepsis where it is characterized by a cascade of events that includes endotoxin uptake by CD14 receptors in the monocytes and subsequent release mediators (cytokines) into the systemic circulation, major biological effects including vaso-permeabilization, hypotension and shock, with significant clinical consequences.[8]

In end-stage renal disease (ESRD) patients are stable but they may still suffer from a condition of chronic or subclinical inflammation leading to cardiovascular complications, progressive malnutrition, and death.[9] In these patients, the phenomenon is due to uremia retention molecules not adequately cleared by current dialysis techniques and a state of smoldering inflammation with increased concentrations of middle-to-large molecular species including cytokines, acute phase proteins, light chains and others.[10–13]

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There are several reasons why hemodialysis patients are subject to chronic inflammation. The condition of uremia per se is characterized by a series of metabolic disturbances that produce an imbalance between immune-stimulation and immune-depression. There is a disequilibrium between production of reactive oxygen species (ROS) and antioxidant defense of the organism. Furthermore, the hemodialysis technique can be responsible of an inflammatory condition due to possible contamination of the hemodialysis fluid, membrane bio-incompatibility and extracorporeal shear stress on blood cells. This may also be exacerbated by other patient-related factors such as infections, periodontal disease, and atherosclerosis [Table 1].

Despite recent improvements in dialysis technology, cardiovascular disease still remains the main cause of morbidity and mortality in ESRD. Traditional risk factors include hypertension, chronic heart failure, dyslipidemia, obesity, tobacco smoking and diabetes. Further risks, however, have recently been shown to be involved including chronic inflammation, oxidative stress, advanced glycosylation end products (AGEs) formation, malnutrition, Ca-P product, endothelial dysfunction and hyper-homocysteinemia.[9,14]

All these risks factors combine their action to produce medium to long-term clinical complications and unsatisfactory outcome. In particular, the retention of uremic toxins in the middle-to-high molecular range and the concomitant activation of the inflammatory cascade may result in further activation of cytokines, acute phase reactants (C-reactive protein [CRP], fibrinogen, serum amyloid A [SAA], transferrin) and damage-associated molecular patterns (DAMPS) causing a cascade of events including endothelial dysfunction, accelerated atherogenesis and cardiovascular complication.[15]

Mortality, morbidity, and hospitalization positively correlate with specific compounds (CRP, SAA, parathyroid hormone [PTH] and beta-2 microglobulin [β2M]) and with cytokines that regulate their metabolism (such as interleukin-6 [IL-6]).[16] β2M and PTH seem to be activated by the inflammatory process, but they could also be active participants in the process. Stevinkel *et al*.[17] have demonstrated significantly different outcomes in patients with CRP above or below 10 mg/L. Kaysen *et al*.[18] have also demonstrated that longitudinal variations in albumin concentration correlate with CRP levels, suggesting that malnutrition is a condition induced by chronic inflammation. In conclusion, ESRD patients are at risk for cardiovascular disease and early atherosclerotic lesions seem to contribute to negative outcomes. In conclusion, a chronic status of inflammation, although often subclinical, has been demonstrated in patients undergoing chronic hemodialysis. Several factors [Table 1] may mediate biochemical and physical processes that activate an inflammatory response in the patient, and subsequently influence outcomes.

In physiological conditions, pro and anti-inflammatory mediators are in a continuous equilibrium. In critically ill patients with sepsis, the overproduction of mediators generates systemic effects including endothelial damage, hemodynamic shock, and vaso-paralysis. At the same time, monocytes present a profound depression of their capacity to respond to different stimuli up to a complete immuno-paralysis.[19] In ESRD, the chronic presence of uremic toxins disrupts the immunological homeostatic balance in a less acute, but still insidious mode.

Table 1

Chronic inflammation in maintenance hemodialysis.

Patient-related and/or endogenous causes	Treatment-related issues
Age, gender and race	Repeated vascular access puncture
Decreased endogenous cytokine clearance	Indwelling temporary catheters
Reduced metabolism of AGEs	Presence of prosthetic devices
Increased cytokine synthesis	Repeated contact with dialysis membrane and tubing
Gene polymorphism (differences)	Back-transport of pyrogens from dialysate
Chronic heart failure, atherosclerosis	Oxidative and carbonyl stress
Chronic infections or localized infections (catheters)	Type of membrane
Periodontal disease	Type of technique

AGEs, advanced glycosylation end products.

This condition leads to a subclinical battle within the organism in which phases of inflammation are followed by phases of immunodepression and cell hypo-responsiveness.[20] While the former phases increase cardiovascular abnormalities and malnutrition, the subsequent phases lead to an impaired response to bacterial invasion and easy occurrence of infections. These factors result in subsequent phases of inflammation and immuno-depression while the patient enters a slippery slope of progressive clinical impairment. This process may take several years but it is documented by subsequent episodes of acute inflammation and infections, cardiovascular events and hospitalization, malnutrition, and progressive reduction in body mass. Thus, there is a paradox where a chronic inflammatory state leading to complications and immuno-depression facilitate infection, coexist in patients on dialysis. The clinical effects of these two entities is an increased cardiovascular risk with progressive cardiovascular disease, and a series of infections that periodically stimulate a new inflammatory cycle. There are now several lines of evidence that retention of uremic toxins may affect this process by blockade of enzymatic pathways, altered monocyte function and activation of complex protein pathways.[21] Such toxins are not effectively removed by current dialysis techniques.[22] Thus, a more adequate extracorporeal therapy should be prescribed and delivered to mitigate the systemic inflammatory response syndrome-compensatory anti-inflammatory response syndrome (SIRS-CARS) condition through an effective removal of uremia retention molecules insufficiently cleared by the classic dialysis techniques.

THE RATIONALE FOR COMBINING HEMOADSORPTION WITH HEMODIALYSIS

Given that most uremia retention toxins and DAMPS are in the molecular weight range of 10 to 50 kDa, current dialysis techniques based on membrane separation processes (relying on diffusion and convection) are unable to effectively remove them.[22] Although more efficient, techniques have been developed such as hemodiafiltration (HDF) or expanded hemodialysis (HDx),[23,24] full correction of uremia retention syndrome has not been achieved yet and thus, new therapeutic options are required.

New sorbent materials with enhanced porosity and biocompatibility characteristics have become recently available.[25] The sorbent is composed by a mixture of styrene and divinylbenzene

with a specific porosity generated during the beads formation. Biocompatible coating ensures adequate hemocompatibility and absence of side effects.[26] Aspecific adsorption of molecules in the range of 10 to 50 kDa occurs by Van der Waals forces, ionic bonds, and hydrophobic bonds.[27] These characteristics allow to overcome the limitations imposed by classic and innovative dialysis membranes and permit to reduce the peaks of chemical mediators and middle-to-high molecular weight toxins involved in signs and symptoms of uremic intoxication [Figure 1]. Furthermore, the simultaneous clearance of circulating cytokines both in the pro and anti-inflammatory side, may allow for a re-equilibration of the immuno-homeostasis.[28] Interesting results have been achieved in randomized controlled trials combining hemoadsorption with hemodialysis (hemoadsorption combined with hemodialysis [HA-HD]).[29,30] Independently on the hemodialyzer utilized, the sorbent cartridge HA 130 (Jafron Medical, Zhuhai, China) placed in series before the dialysis filter, has demonstrated remarkable efficacy in reducing the levels of β2M, PTH, Cytokines and other retention molecules with significant improvement of several different symptoms and clinical outcomes [Table 2]. This has led to consider HA-HD as a new option for ESRD patients with symptoms and complications.[31] Analyzing the results obtained in these papers and in our own experience, on the kinetics of β2M in a single session, in a series of three consecutive sessions of a week and in the last week of each month for three months using different frequencies of application (first month: Three sessions per week; second month: Two sessions per week; third month: One session per week), and integrating those date with previously achieved results,[29,30,32–36] we were able to formulate a possible hypothesis on the beneficial effect of combining hemoadsorption with hemodialysis.

THE INFLAMMATION MITIGATION HYPOTHESIS (IMH)

The peak concentration theory published several years ago,[37–39] despite being conceived in acute illness, may result particularly useful to study new techniques of blood purification (such as hemoadsorption) and their effects on the immunological homeostasis of the maintenance hemodialysis patient. According to the theory, immuno-dysregulation induced by different clinical conditions may lead to peak concentrations of pro- and anti-inflammatory mediators. The impact of a single drug may not be able to cope with the multitude of molecules involved in the process. On the other hand, a non-specific removal of mediators may instead preferentially remove molecules with higher concentration leading to a re-equilibration of the immuno-homeostasis [Figure 1]. We have compared the behavior of β2M in

Table 2

HA-HD: Indications/benefits.

HA-HD indications	Documented effects
	Improvement in
Chronic Inflammation	Appetite/nutrition
β2M accumulation	Muscular strenght
Anorexia, malnutrition	Cogntitive function
Uremic pruritus	Pain relief
Uremic symptoms	Sleep quality
Muscular weakness	Blood pressure control
Sleep disorders	Quality of life
Osteo-articular pain	/

β2M, beta-2 microglobulin; HA-HD, hemoadsorption combined with hemodialysis.

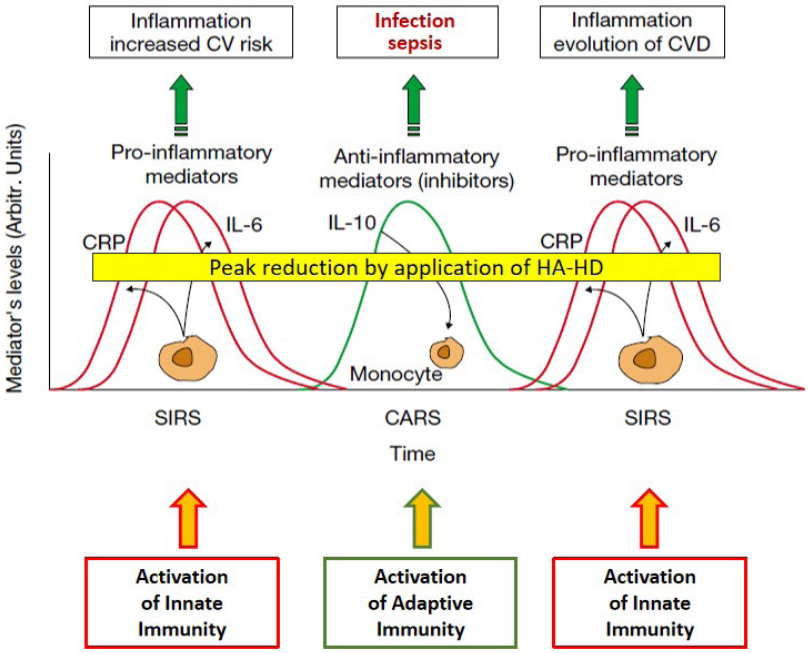

Figure 1. The diagram describes the alternate increase in concentration of pro-inflammatory and anti- inflammatory mediators in patients undergoing maintenance hemodialysis. This phenomenon, induced by uremic toxins not adequately cleared by current dialysis techniques, may be responsible for a continuous activation of a smoldering subclinical inflammation and immunological dysfunction, with the consequence of accelerated atherosclerosis and increased cardiovascular risk on one side, and the high incidence of infection and sepsis on the other side. The application of HA-HD may contribute to eliminate the peaks of different mediators together with the causative mechanism induced by uremic toxins, restoring a more physiological level of immune-homeostasis. CV, cardiovascular; CVD, cardiovascular disease; CRP, C-reactive protein; IL, interleukins; HA-HD, hemoadsorption combined with hemodialysis; CARS, compensatory anti-inflammatory response syndrome; SIRS, systemic inflammatory response syndrome.

a single session of HA-HD with a single session of HD and HDF calculating single and double pool kinetics [Figure 2]. HA-HD appears to be more effective achieving lower concentrations of β2M at the end of a four-hour session. Considering a volume of distribution of 16%–18% of the body weight, a post-dialytic rebound in plasma is expected [Figure 2 left panel]. Nevertheless, In the right panel of Figure 2 we can observe a progressive reduction of pre-dialysis values when the technique is applied in a 3 sessions/week (s/w) regime. This observation is compatible with a progressive reduction of the β2M pool in the distribution volume due to increased removal during HA-HD. Interestingly enough, studying the behavior of β2M over three months with a progressive reduction of the frequency of application of the HA 130 cartridge from three to one session/week, we can observe a reduction of the time average concentration (TAC) with a maintenance of the lower concentration even with one single session per week of HA-HD [Figure 3]. Considering that β2M concentration is dependent on the balance between removal and generation in a stable distribution volume condition, we must assume that after the attack (3 s/w) and the stabilization phase (1 s/w), one single session of HA-HD plus 2 s/w or regular high flux dialysis or HDF, allows to maintain permanent lower concentrations of β2M in comparison with the standard treatment. This phenomenon may be explained by a concomitant reduction in generation as hypothesized in Figure 4. In fact, while the insufficient clearance and consequent retention and accumulation of uremic toxins may enhance the inflammatory pattern of the organism and the increased generation of β2M, the improved clearance of β2M together with the removal of middle-to-large molecules involved in inflammation, may contribute to ameliorate the inflammatory status of the patient, and reduce the generation of β2M [Figure 4].

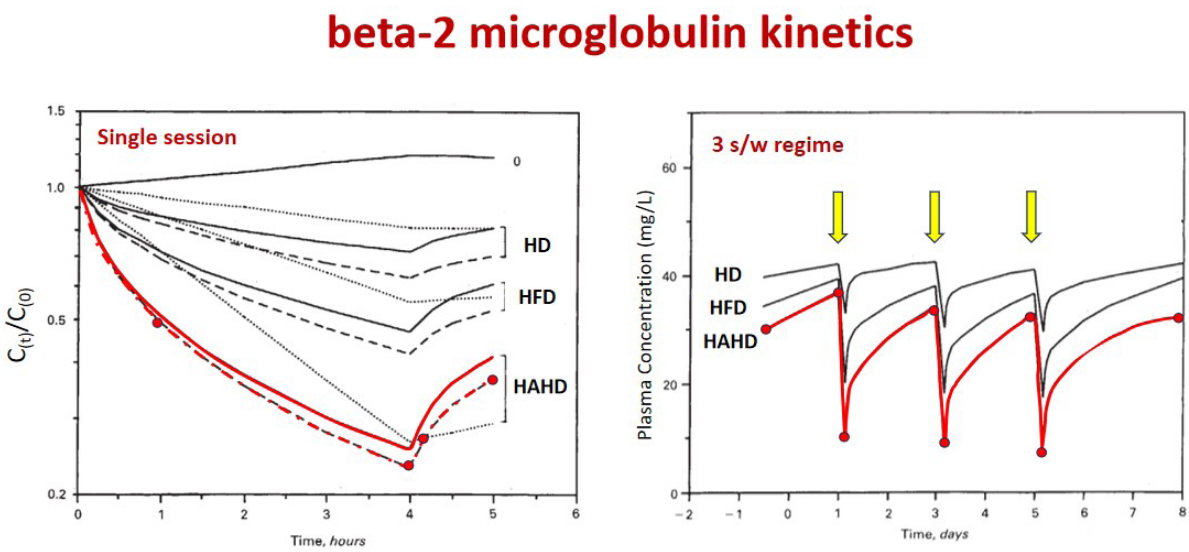

Figure 2. Behavior of β2M concentrations in a single session of HA-HD, and HFD or HDF. Different lines for each technique describe single and double pool kinetics considering a distribution volume for β2M of 16%–18% of body weight. The number 0 describes progressive accumulation in the absence of any blood purification technique and allows to estimate the generation rate (values integrated from current and previous observations.[29–36] β2M, beta-2 microglobulin; HDF, hemodiafiltration; HFD, high flux hemodialysis; HA-HD, hemoadsorption combined with hemodialysis; s/w, sessions/week.

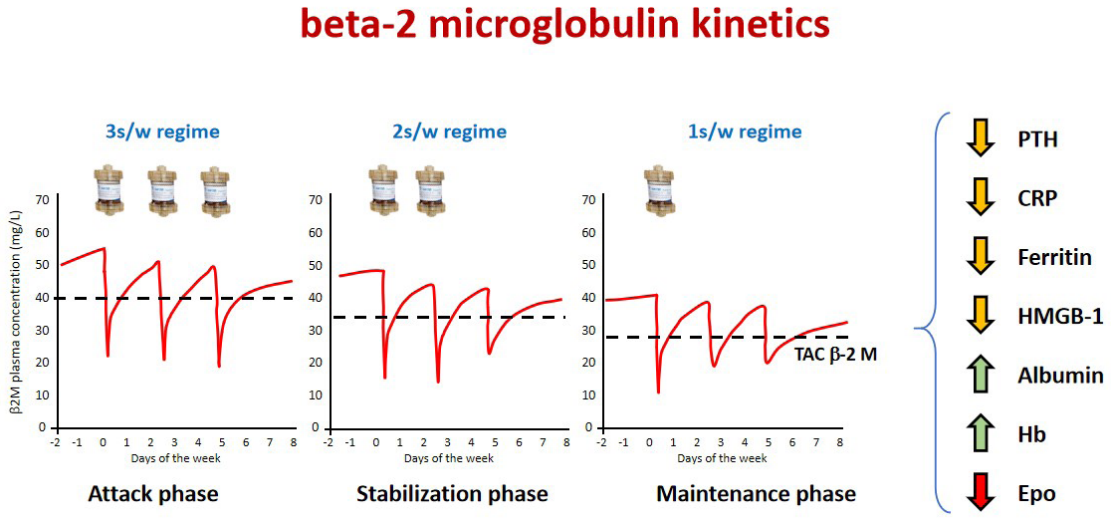

Figure 3. Kinetic calculation of time average concentration of β2M in a progression of regime adaptation from 3 to 1 s/w of HA-HD. Maintenance values with 1 s/w regime are derived from published data.[29–36] β2M, beta-2 microglobulin; PTH, parathyroid hormone, CRP, c-reactive protein; HMGB-1, high mobility group box 1 protein; Hb, hemoglobin, Epo, erythropoietin, HA-HD, hemoadsorption combined with hemodialysis; s/w, sessions/week. TAC, time average concentration.

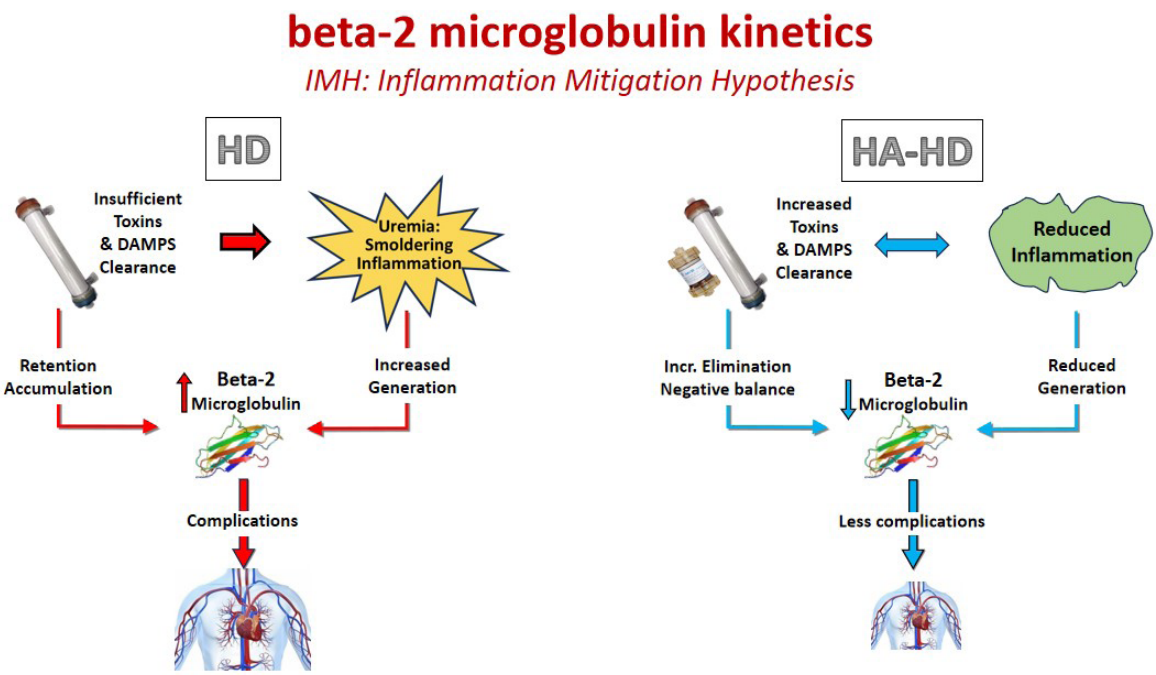

Figure 4. The inflammation mitigation hypothesis is graphically depicted. In the left panel the insufficient removal of uremic toxins and DAMPS leads to accumulation of uremic toxins and produce a smoldering inflammatory pattern that enhances β2M generation. The consequence is a progressive increase of β2M in plasma with the well-known clinical consequences. In the right panel a different situation is described. The enhanced clearance of toxins and mediators leads to an increased elimination of β2M together with a reduction of the inflammation, responsible for increased β2M generation. The observed effect is a reduction of the plasma levels of β2M and a lower rate of complication as described in published data.[29,30] β2M, beta-2 microglobulin; HDF, hemodiafiltration; DAMPS, damage-associated molecular patterns. HA-HD, hemoadsorption combined with hemodialysis.

CONCLUSIONS

HA-HD appears to be a reliable technique to improve uremic symptoms and to correct the imbalance of the immuno-response in chronic maintenance dialysis patients. In the single session the reduction ratio for β2M appears superior to other techniques such as high-flux hemodialysis (HFD) or hemodiafiltration (HDF). In the thrice weekly regime, the TAC of β2M results lower than in HFD and HDF. In the long term, a lower concentration of β2M seems to be maintained even with a 1 s/w regime. Considering the parallel reduction of inflammatory parameters, typically observed in HA-HD [Figure 3], we could hypothesize that the enhanced removal of uremic toxins and chemical mediators leads to a mitigation of the systemic inflammation with a progressive reduction in the generation of β2M. Thus, even in presence of 1 s/w of HA-HD and two regular HD or HDF s/w in the maintenance phase, the plasma levels of β2M remain constantly low due to the lower generation induced by a reduction of the systemic inflammation. This IMH supports the prescription of HA-HD 1 s/w, possibly after a month of 3 s/w regime in those patients where specific symptoms and biochemical parameters suggest inadequate correction of the uremic syndrome. The hypothesis needs to be tested in the real-world scenario and in a wide spectrum of patients, however the basis and rationale for the clinical application of HA-HD remain and may be the beginning of a new era of kinetic studies in maintenance hemodialysis patients with symptoms and complications.

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Authors contribution

All authors contributed to the discussion, preparation, and the content of the manuscript.

Ethics approval and consent to participate

Not applicable.

Conflicts of interest

Claudio Ronco has been advisor or member of the speaker bureau or received honoraria for presentations in the last 3 years from the following companies: Asahi medical, Aferetica, Baxter, Biomerieux, B. Braun, Cytosorbents, Fresenius medical care, Medtronic, Jafron Medical, ESTOR, Nipro, Medica, GE. All other authors declared no conflicts of interest.

Data availability statement

No additional data.

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