Protein-Bound Uremic Toxin in Chronic Kidney Disease

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Uremic toxins (UTs), particularly protein-bound uremic toxins (PBUTs), accumulate in chronic kidney disease (CKD) patients, causing significant health complications like uremic syndrome, cardiovascular disease, and immune dysfunction. Innovations such as online hemodiafiltration aim to enhance the removal process, while novel adsorptive therapies offer a means to address the high affinity of PBUTs to plasma proteins.

Keywords: chronic kidney disease ; uremic toxins ; protein-bound uremic toxins ; adsorptive therapies

1. Introduction

Chronic kidney disease (CKD), a global health challenge, impacts an estimated 10–15% of the world's population [1]. In 2017, around 843.6 million individuals were affected, as recent studies on the global CKD prevalence indicate [2]. This rise is partly attributed to the increased incidence of diabetes, hypertension, obesity, and aging populations [3], alongside improved access to renal replacement therapies in economically developing nations [4].

CKD stages are independently linked to heightened cardiovascular event risks, decreased quality-adjusted life years, and high morbidity and mortality rates. From 1990 to 2017, the CKD-related global mortality surged by 41.5%, ranking it as the 12th leading death cause worldwide [5]. By 2040, it is projected to become the 5th leading cause of global mortality [6].

One CKD consequence is the gradual decline of glomerular filtration, leading to metabolic waste product accumulation in the bloodstream, known as uremic toxins (UTs). These toxins are associated with the uremic syndrome, presenting symptoms like nausea, vomiting, asthenia, anorexia, and pruritus due to their detrimental pathophysiological effects [7].

2. Effects of Protein-Bound Uremic Toxins

Protein-bound uremic toxins (PBUTs) are not merely waste products; their accumulation in chronic kidney disease (CKD) can lead to a range of systemic effects. These toxins, particularly notorious for their harmful influence on various tissues, significantly impact the cardiovascular system. Studies have elucidated the multifaceted roles of PBUTs in instigating renal fibrosis, vascular calcification, anemia, peripheral arterial disease, adynamic bone disease, insulin resistance, malnutrition, and immune system deficiency [7][8].

- Endothelial Dysfunction: Endothelial dysfunction caused by PBUTs is closely related to the development of cardiovascular diseases in patients with chronic kidney disease. PBUTs can cause structural damage, inflammation, and a decrease in endothelium-dependent vasodilation [9][10]. Furthermore, endothelial dysfunction is associated with the progression of chronic kidney disease and albuminuria [11]. Patients undergoing dialysis for chronic kidney disease exhibit a markedly diminished endothelial response to stimuli when compared to a control group of healthy individuals. This reduced response is evident across various assessment parameters, including both shear stress and biochemical agents, indicative of compromised endothelial function [12]. PBUTs can decrease nitric oxide production in endothelial cells by inhibiting endothelial nitric oxide synthase (eNOS) activity and expression [13]. PBUTs, like indoxyl sulfate, act as prooxidant and proinflammatory agents, which are associated with changes in the hemostatic system, increased oxidative stress, and monocyte activation. Additionally, this leads to a prothrombotic state through the activation of prothrombotic factors such as tissue factor and factor Xa [14], and the formation of endothelial microparticles.

High levels of indoxyl sulfate (IS) and p-cresol sulfate (PCS) in the serum have been used to predict cardiovascular events and are also implicated in vascular disease, including arteriosclerosis, endothelial inflammation, oxidative stress, and vascular calcification [15].

Most cardiovascular complications associated with chronic kidney disease are secondary to the activation of prooxidative/inflammatory pathways through human AhR activation. PBUTs have been recognized as endogenous agonists of AhR [16]. The aryl hydrocarbon receptor (AhR) is a transcription factor found in the cell's cytoplasm in its inactive form. It has been demonstrated that AhR is more stimulated in stage 3 chronic kidney disease patients, directly associated with higher IS levels and inversely proportional to epidermal growth factor receptor (EGFR) levels [17].

- Prooxidant and Proinflammatory Actions: Indoxyl sulfate acts as both a prooxidant and proinflammatory agent, linked with changes in the hemostatic system, increased oxidative stress, and monocyte activation. This leads to a prothrombotic state through the activation of prothrombotic factors such as tissue factor and factor Xa [14], and the formation of endothelial microparticles.

- Cardiorenal Syndrome: The accumulation of PBUTs, particularly IS, in cardiomyocytes is linked to increased production of inflammatory cytokines such as IL1, IL6, and TNF-α [18]. These toxins have been associated with pro-arrhythmogenic effects and atrial fibrillation [15]. Studies have also noted structural and functional changes in cardiomyocytes, including reduced spontaneous contraction and irregularity, following exposure to toxins like p-cresol sulfate (PCS) [19].

- Immune System Dysfunction: Patients with chronic kidney disease present immune system dysfunction due to various causes, such as the dialysis process, vitamin D deficiency, and a sustained systemic inflammatory state due to elevated PBUT, which can alter the innate immune response [20]. Among the main PBUTs related to immune system activation are IS, PCS, and p-cresyl glucuronide, among the most well-known [21][22].

IS acts as a prooxidant and proinflammatory agent, triggering immune responses and stimulating chronic kidney disease progression. Increased plasma IS has been associated with changes in the coagulation cascade, increased oxidative stress, and monocyte activation [23]. This molecule shows a positive correlation with neopterin, a molecule generated by macrophages and monocytes after being stimulated by IFN-gamma produced by activated T cells. As a result, a high production of reactive oxygen species (ROS) and an increase in the expression of cell adhesion molecules (CAM) can be observed, promoting monocyte–endothelial cell interaction, leading to vascular inflammation and endothelial dysfunction. PBUTs affect both the innate and adaptive immune systems through multiple mechanisms, resulting in the development of systemic pathologies in humans, highlighting the importance of studying them, and advancements in this field would greatly improve the clinical management of these patients.

Kidney

Accumulation of indoxyl sulfate (IS) can lead to the deterioration of the remaining renal nephrons, primarily within proximal tubular cells, thereby stimulating glomerulosclerosis, renal fibrosis, and the progression of chronic kidney disease (CKD). This process contributes to an increased expression of pro-collagen alpha 1, transforming growth factor beta 1 (TGF-β1), and tissue inhibitor of metalloproteinase 1 (TIMP-1) genes, resulting in further nephron loss and thereby accelerating CKD progression [24]

There is evidence that elevated levels of p-cresyl sulfate (PCS) in the kidneys lead to increased expression of proinflammatory cytokines and genes in renal tubular cells, along with activation of the renin–angiotensin–aldosterone system (RAAS) and epithelial–mesenchymal transition, culminating in fibrosis and nephrosclerosis [25]. Moreover, elevated PCS levels are associated with reduced Klotho expression through methylation of the Klotho gene, contributing to renal cell senescence [26].

3. Protein-Bound Uremic Toxin Clearance Strategies

Conventional dialysis remains the primary treatment modality for patients with end-stage chronic kidney disease (CKD). Nevertheless, the effective removal of protein-bound uremic toxins (PBUTs) presents a significant challenge in these patients, attributed to their high affinity for protein binding. This limitation is not adequately addressed by current conventional methods. There is a scarcity of long-term evidence, as most efforts to enhance the clearance of these toxins remain experimental. Furthermore, regarding the techniques currently employed, such as prolonged and frequent dialysis, there are no comprehensive studies that evaluate the long-term outcomes of PBUT removal in comparison to other techniques [27].

3.1. Conventional Dialysis Efficacy on Protein-Bound Uremic Toxins (PBUTs)

Conventional dialysis methods, including hemodialysis and peritoneal dialysis, have not been proven effective in significantly reducing the levels of PBUTs [28][29]. When focusing on protein-bound toxins, it becomes evident that they

play a critical role in patients undergoing dialysis due to the inability of the dialysis membrane to filter them effectively. Various studies have focused on this issue, adopting different approaches [30]. Although advancements in membrane technology and purification techniques have shown varying degrees of success in decreasing the free fraction of certain toxins, the clinical significance of these reductions remains under active investigation. Some membranes, especially those with high sieving coefficients, have been promising in enhancing toxin purification. However, their overall efficacy varies depending on the toxin type and clinical scenario [31].

It appears that no membrane or technique, regardless of its high sieving coefficient, has been able to adequately purify these toxins. They may demonstrate a reduction in the free fraction, but this represents a very modest clinical impact, as the free fraction constitutes a minimal portion of the total toxin amount. However, the use of albumin in dialysate, by promoting binding with a high flow, demonstrates that standard dialysis membranes are not the limiting factor due to the low molecular weights of PBUTs but rather its protein binding [31].

In recent years, the clearance profiles of state-of-the-art hemodialysis membranes have seen significant improvements. Several characteristics must be considered in the evaluation of new membranes. These include new permeability rates, the hydrophilic or hydrophobic nature of the membranes, adsorption capacity, and electrical potential [32]. Additionally, the onset of molecular weight retention, molecular weight limit, and mass transfer area coefficient must be measured [33].

Conventional dialysis poorly clears them because only the free solute portion contributes to the concentration gradient that drives their diffusion from plasma to dialysate. The extent to which protein binding limits the removal of PBUTs depends on multiple factors, including the dialyzer size, dialysate flow, and the strength of the protein binding itself. Despite the rapid dissociation of PBUTs from albumin, studies by T. Meyer demonstrate that significantly increasing the dialysate flow with standard dialyzers can approximately quadruple the PBUT removal [31].

3.2. Conventional Dialysis: Importance of Dialysis Time

One of the most crucial factors in the efficacy of uremic toxin elimination is the dialysis time. The duration of the dialysis session is a critical determinant to ensure adequate clearance. Generally, longer dialysis sessions allow for more effective removal of PBUTs [34]. The reason is that the small-sized free fraction is cleared, balancing with the albumin-bound fraction released from anchoring to maintain the free fraction ratio. The longer the hemodialysis (HD) session, the progressively more free fraction is cleared. The clearance is the same per minute but is more constant and frequent [27]. Dissociation of the protein-bound form requires time; a conventional dialysis session is too short to prevent the new equilibrium of PBUTs strongly bound to albumin [35]. But to drive this transfer, what is needed is merely more clearance of the free fraction of the PBUTs within the dialyzer (as with more frequent dialysis with the same blood, more time on dialysis, or increasing the dialysate flow). PBUTs' clearance increases when the free form is removed in long conventional dialysis, while it does not change with extended convective dialysis [36]. Association/dissociation of PBUTs and albumin happens during the time of blood passing through a hollow fiber dialyzer, when a strong chemical gradient is promoted by a rapid dialysate flow.

Prolonging the HD time through extended nocturnal HD removes a larger amount of PBUTs. Cornelis et al. observed higher PCS and IS clearance in long nocturnal dialysis, although the plasma concentrations did not change when the HD duration increased from 4 to 8 h [37]. Much of the problem is also in the slow diffusive transfer of PBUTs and mid-large dialysate toxins from cells to interstitium to blood. Long dialysis also provides time for this transfer [38].

3.3. Importance of Residual Renal Function

Residual renal function is important in reducing PBUTs [39][40]. The native kidney eliminates PBUTs mainly as free forms, while the total forms of IS and pCS are eliminated only 2% and 1.7%, respectively. Dialysis clears the total forms similarly to the native kidney, while it clears only 20–30% of free forms compared to the native kidney [41].

3.4. Online Hemodiafiltration: Role of Convection

Convection increases the elimination of uremic toxins during dialysis, especially medium- or large-sized ones [42]. However, PBUTs' clearance with convective techniques has not shown conclusive data on their efficacy. One study demonstrated a lower pCS concentration and higher elimination in predilutional 60 L online hemodiafiltration compared to postdilutional 20 L. In addition to free PBUTs, small-sized toxins, including urea and creatinine, are better eliminated in predilutional HDF than postdilutional [36]. However, another study showed a greater reduction in both free and protein-bound PBUTs in postdilutional online HDF [43].

3.5. Expanded HD

Medium cutoff (MCO) dialyzers, also known as expanded dialysis, cannot increase PBUT elimination [44][45].

3.6. Adsorptive Therapies

Adsorptive therapies represent an innovative strategy for addressing uremic toxin removal in CKD patients. Despite their effectiveness, technical complications such as cost, biocompatibility and material saturation limit their use.

These therapies rely on the ability of certain adsorbent materials to selectively capture PBUTs from the bloodstream, not only the free fraction but also the protein-bound fraction, due to their high affinity for these molecules [46].

The mechanism of action involves the interaction between PBUTs and adsorbent materials. When the patient's blood or dialysate flows through an adsorptive therapy device, uremic toxins bind to the adsorbent surface due to chemical and physical forces. Once bound, they do not detach, causing material saturation depending on the surface. Activated carbon's high adsorption capacity and other adsorbent materials have led to a significant reduction in toxin concentrations in CKD patients [47][48][49][50].

Among the adsorbent materials used is activated charcoal, which significantly improves toxin clearance when used simultaneously with conventional HD [51] or with hemo-perfusion [52]. Activated carbon has a high specific surface area and exceptional adsorptive properties [53].

Besides charcoal, many molecules, primarily celluloses or polymers, have been used. Hexadecyl chains immobilized in cellulose pores have been used simultaneously with conventional HD, resulting in a 34% decrease in the free form of IS, while the total IS barely changed [52].

CMK-3 is a silica- and carbon-based nanoporous sorbent [54]. The CMK-3 sorbent presents two different types of pores, micropores and mesopores [55], showing a high adsorption level on the free fraction of PBUTs. In another study [56] with two different resins, one with a sorbent based on divinylbenzene attached to a highly biocompatible polymer and cellulose with hexadecyl chains, showed a significant reduction in the free form rather than the total PBUTs. The difficulty in reducing the total PBUTs could be due to the constant disturbance of the balance between the free and protein-bound forms [35]. Initially, the unbound fraction undergoes elimination, resulting in a disruption of equilibrium between the bound fraction and the extravascular compartments. The dissociation does not occur until the concentration of the unbound fraction decreases, a process that unfolds gradually due to its dialysis over the course of the session. Despite the rapid dissociation capacity of albumin [57], the equilibrium is eventually restored as the bound fraction is gradually released. However, the passage of toxins from the tissue compartment to the blood is very slow and constitutes the most limiting factor. The degree of binding is related to the concentration of PBUTs around the albumin. As the unbound concentration decreases, especially below the dissociation constant level, the PBUTs have to leave the albumin. If a sorbent treatment removes free PBUTs but not the total, it is because the albumin has bound PBUTs in its course around the body. This mechanism may elucidate the augmentation in the binding percentage observed in certain studies, along with the potential modulation of equilibrium by variables such as the pH [35].

Efforts have also been directed toward enhancing this adsorption process through the application of prior plasma separation. While this method has shown promise, it is characterized by its labor-intensive and costly nature [49][50]. T. Meyer has observed that using a conventional high-permeability dialyzer and standard dialysis system provided total solute clearances of about 18 mL/min for p-cresol sulfate, and 19 mL/min for indoxyl sulfate, when dialyzing blood with these tightly bound solutes [31]. The dialyzers with a carbon-block recirculating system had clearances of about 45 mL/min for p-cresol sulfate and 61 mL/min for indoxyl sulfate when operating alone, without removing small toxins such as urea. When operated in series, the clearances of the carbon-regenerated dialysis system and regular dialysis system had clearances for PBUTs that were additive. These clearances were with standard high-permeability dialyzers, and the only change was the increase in dialysate flow rate to 1000 mL/min that is made possible by regeneration of the dialysate by an activated carbon block. So, 80% binding or even 90% is not so high that significant clearances are made impossible with standard dialysis membranes. A high dialysate flow rate maintains the gradient for removal by diminishing the dialysate concentration right at the membrane surface. Suspended charcoal particles in the dialysate can do the same thing as a very high dialysate flow rate [31].

Challenges and Future Directions of Adsorptive Therapies

Despite the promising benefits of adsorptive therapies, there are challenges that must be addressed. These include optimizing adsorbent materials, therapy duration, and managing potential side effects. Furthermore, more research is

needed to fully understand the impact of these therapies on the quality of life of CKD patients [47].

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