

## Review Article

# Renal Replacement Modality Affects Uremic Toxins and Oxidative Stress

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Nowadays, the high prevalence of kidney diseases and their related complications, including endothelial dysfunction and cardiovascular disease, represents one of the leading causes of death in patients with chronic kidney diseases. Renal failure leads to accumulation of uremic toxins, which are the main cause of oxidative stress development. The renal replacement therapy appears to be the best way to lower uremic toxin levels in patients with end-stage renal disease and reduce oxidative stress. At this moment, despite the increasing number of recognized toxins and their mechanisms of action, it is impossible to determine which of them are the most important and which cause the greatest complications. There are many different types of renal replacement therapy, but the best treatment has not been identified yet. Patients treated with diffusion methods have satisfactory clearance of small molecules, but the clearance of medium molecules appears to be insufficient, but treatment with convection methods cleans medium molecules better than small molecules. Hence, there is an urgent need of new more validated, appropriate, and reliable information not only on toxins and their role in metabolic disorders, including oxidative stress, but also on the best artificial renal replacement therapy to reduce complications and prolong the life of patients with chronic kidney disease.

## 1. Introduction

As a result of the deterioration of kidney function, patients with chronic kidney disease develop conduction, accumulation of toxic substances called uremic toxins and related symptoms. In dialyzed patients, the development of sarcopenia and deterioration in nutritional status may be associated with increased mortality [1–3].

The development of chronic inflammation is associated, among other things, with the accumulation of uremic toxins and activation of neutrophils and monocytes, and the production of proinflammatory cytokines and reactive oxygen species increases oxidative stress [3, 4]. In patients with chronic kidney disease, IL-6 and CRP may play a major role in the pathophysiology of inflammation, and in dialyzed patients also, IL-1, 2, 4, 5, 6, 8, 12, and 13 and tumor necrosis factor-alpha (TNF-alpha) seem to be important [3–5].

The emerging chronic inflammation (increase in CRP and IL-6 concentration) is proportional to the severity of

chronic kidney disease and may cause the development of cardiovascular diseases and may affect renal function, because oxidative stress damages the endothelium and develops atherosclerotic lesions in the blood vessels [4–6].

## 2. Uremic Toxins and CKD

Among uremic toxins, there are 3 main groups that differ in size, protein-binding ability, and hydro- and lipophilicity. For this reason, these substances have different importance, and the possibility of their elimination from the patient's body depends on the physicochemical characteristics of these substances [7, 8]. In their work, La Manna and Ronco paid attention not only to the size but also to the structure of the particles. The virtual molecular radius (Einstein-Stokes radius) or the radius of the ball describing the molecule may be important for the rate of substance removal due to changes in diffusion coefficient and screening values [8].

Small hydrophilic particles with a molecular weight of up to 500 Da, not bonded to proteins, form a seemingly homogeneous group of substances. The best known example of this group is urea; the high concentration of which leads to an increase of osmotic pressure, impaired nitric oxide synthesis, proinflammatory endothelial dysfunction and apoptosis, and death of smooth muscle cells [9–11]. Other substances, such as guanidine, may competitively inhibit NO synthase and contribute to the development of hypertension, progression of renal failure and renal fibrosis, and to adverse cardiovascular events and increased mortality in patients with renal failure [12–14].

The adverse clinical effects of protein-related toxins, including indoxyl sulfate (IS) and p-cresol sulfate (p-CS), mostly concern glomerulosclerosis, interstitial fibrosis, and deposits in the extracellular renal matrix [15, 16]. Atherosclerotic lesions are also developed [17]. These toxins activate the transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) and kappa B nuclear factor (NF- $\kappa$ B), which reduce Klotho protein expression, as well as the formation of free oxygen radicals (e.g., by increasing the production of NAD(P)H oxidase and reducing glutathione) [16, 18]. Additionally, epithelial cells are inducted into mesenchymal cells and renin-angiotensin-aldosterone system is activated [19].

The last group of toxins consists of middle molecules. Similar to the previous groups, they may cause various biochemical and metabolic disorders, which will intensify the inflammation and damage the blood vessel wall [20]. Glorieux et al. [21] investigated the serum beta2-microglobulin (B2MG) and advanced oxidation protein products (AOPP) as middle molecule uremic toxins and protein carbonyl (PCO) as oxidative stress marker in uremic patients undergoing high-flux versus low-flux hemodialysis (HD). They showed that high-flux HD results in reduction of some of the middle molecule toxins and protein carbonyl levels better than low-flux HD, and was associated with a better response to erythropoietin. The HEMO study confirmed the beneficial effect of removing mid-sized uremic toxins on patient survival, and beta2-microglobulin concentrations had a significant impact on patient mortality [22, 23]. In patients undergoing long-term dialysis, beta2-microglobulin deposits can be found in tissues, which some researchers associate with the development of vascular disease and activation of inflammatory markers such as TNF-alpha and IL-6 [24, 25]. Other important mid-sized toxins include advanced glycosylation end products (AGEs), which in patients with chronic kidney disease are formed as a result of carbonyl stress [26]. An increase in their concentration results in an increased inflammatory reaction and inactivation of nitric oxide and tissue damage [7]. In patients with diabetes, the formation of glycosylation end products amplifies tissue damage and impairs their functions [27].

### 3. Oxidative Stress and Chronic Kidney Disease (CKD)

Excessive production of reactive oxygen species (ROS) in cell mitochondria by cytochrome oxidase enzymes or failure of antioxidant mechanisms leads to oxidative stress, resulting

in changes in the structure and function of various biomolecules which may aggravate atherosclerotic lesions and accelerate organ damage, including kidney damage [28, 29].

Due to the increase in nicotinamide adenine dinucleotide phosphate oxidase (NADPH) activity and decrease in superoxide dismutase (SOD) activity already in stage 3 chronic kidney disease (CKD), there may be an increase in superoxides ( $O_2^-$ ), which are the cause of peroxynitrite (ONOO $^-$ ) and hypochlorous acid (HOCl) formation, and carbonyl stress is the cause of inflammation [28].

In addition, elevated levels of endogenous nitric oxide inhibitors (NOS), including asymmetric dimethylarginine (ADMA), in the endothelium of patients with chronic kidney disease decrease the bioavailability of nitric oxide (NO). The abovementioned pathways may cause vasoconstriction, hypertension, development of end-stage renal disease (ESRD), cardiovascular events, and neurological and immunological complications [30, 31]. Reduced ADMA level can delay kidney function loss in CKD patients [32].

As mentioned above, 4 major oxidative stress pathways are known: the classical pathway, associated with an imbalance between NADPH and SOD, the nitrosative and chloride pathways, associated with the synthesis of ONOO $^-$  and HOCl, respectively, and the carbonyl pathway, associated with increased production of AGEs [28, 33] (Figure 1).

In elderly patients, as well as those with chronic renal failure, diabetes, or chronic inflammation, neutrophils and phagocytes are activated and ROS are increased. Similarly, HD and PD treatments may increase  $O_2^-$ , which is associated with the use of bioincompatible accesses, membranes, and dialysis solutions. Furthermore, uremic toxin accumulation can simultaneously activate the prooxidant system and inhibit the antioxidant system [28, 34–37] (Figure 1).

ROS activation results in the activation of oxidative stress pathways, and the development of chronic kidney disease due to glomerular damage and renal parenchymal fibrosis, and various comorbidities such as atherosclerosis [32].

### 4. Endothelial Damage in Chronic Kidney Disease (CKD)

The endothelium is a physical barrier, which affords movement of small solutes in preference to large molecules through vessel wall; therefore, it is involved in tissue autoregulation, regulating cellular and nutrient trafficking. The endothelial cells mediate vasoactivity. Normally, the endothelium maintains the vessel in a relatively dilated state. Secretion of nitric oxide, and in minor extent of prostacyclin, C-type natriuretic peptide, and different endothelial-derived hyperpolarizing factors by endothelial cells gives the vasodilation effect; however, the endothelium can secrete also several vasoconstrictor substances including thromboxane A<sub>2</sub>, endothelins, angiotensin II, and reactive oxygen species [38–40]. The endothelium maintains the local balance between pro- and anti-inflammatory mediators, i.e., ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular adhesion molecule-1), E-selectin, nitric oxide, and nuclear factor  $\kappa$ B (NF- $\kappa$ B), and interacts with circulating blood cells, i.e., mediates adherence of leukocytes and platelets to the

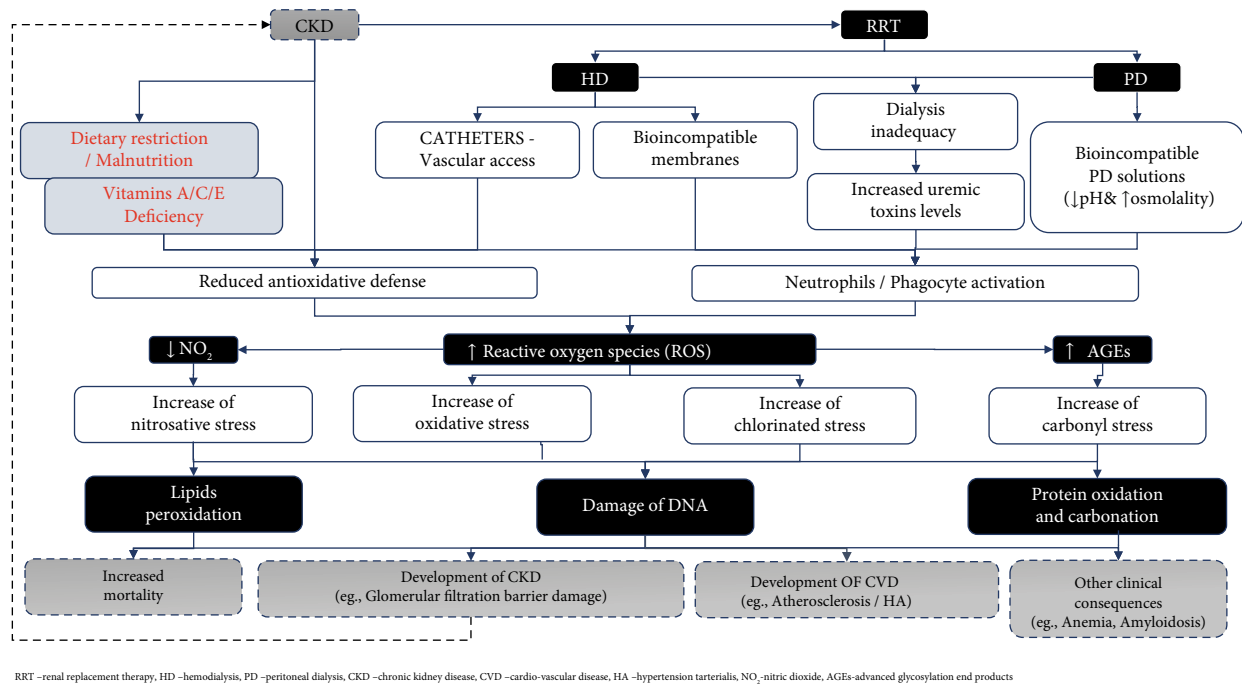


FIGURE 1: Endothelial dysfunction in patients with chronic kidney disease with its complications. RRT: renal replacement therapy; HD: hemodialysis; PD: peritoneal dialysis; CKD: chronic kidney disease; CVD: cardiovascular disease; HA: arterial hypertension; NO<sub>2</sub>: nitric dioxide; AGEs: advanced glycosylation end products.

vessel wall during injury and inflammation [38–41]. The endothelial cells also maintain the local balance between procoagulant and anticoagulant factor activities, i.e., nitric oxide and prostacyclin which inhibit platelet aggregation, thrombomodulin which inactivates thrombin, and others: plasminogen activator (t-PA), its inhibitor (PAI-1), von Willebrand factor (vWF), thromboxane A<sub>2</sub>, tissue factor pathway inhibitor (TFPI), and fibrinogen [38–41]. The endothelium is also involved in new blood vessel generation—angiogenesis. Endothelial cells are heterogeneous, which allow regulation of their activity and functions in specific places, i.e., in the glomeruli [42]. Generally, the steady-state endothelial cells have a vasodilatory, antiadhesive, and anticoagulant phenotype, whereas the activated endothelium has vasoconstricting proadhesive and procoagulant character [38, 43]. In patients with CKD, endothelial cell damage is connected to disturbances in vasorelaxant, anti-inflammatory, and antithrombotic activities due to reduced level of nitric oxide [44].

In clinical practice, there are no reliable markers of endothelial dysfunction, so confirmation of its disorders seems to be difficult. On the other hand, the intact endothelium might initiate or progress the disease. Progressive endothelial damage in the renal medullary capillary system may be the cause of progressive renal injury, and chronic renal failure may develop endothelial dysfunction and atherosclerosis and can lead to higher cardiovascular mortality and development of microalbuminuria and renal failure in CKD patients [45, 46].

## 5. Oxidative Stress Induction by Uremic Toxins

Decreased renal function leads to development of inflammation due to longer half-lives of proinflammatory markers and

biochemical markers of endothelial dysfunction, e.g., IL-6, CRP, and TNF- $\alpha$  [5, 47, 48]. Together with progression of renal failure, higher activity of soluble adhesion molecules (ICAM-1, VCAM-1, and vWF) and matrix metalloproteinases can be observed due to activation of NF- $\kappa$ B pathway and decrease of Klotho protein [49–51]. In the majority of patients with CKD, alterations in calcium-phosphate balance are present. High phosphate levels can suppress endothelial NO synthase and increase ROS formation [52]. Endothelial cell dysfunction in uremia can also be associated with low triiodothyronine level which can change ADMA effect on endothelial function [53, 54]. Increased AGE and decreased soluble AGE receptor levels in patients with renal failure can change glycation processes and increase atherosclerotic formation [55, 56].

## 6. Uremic Toxins and Renal Replacement Therapy

In patients with end-stage renal failure, the initiation of renal replacement therapy and reduction of uremic toxin concentration as a result of such treatment may be important to reduce inflammation, although on the other hand, it may also exacerbate inflammation, e.g., due to infections [34]. Renal replacement therapy may also intensify the oxidative stress generated by urea, but the mechanism depends on the type of dialysis: hemodialysis (HD) increases lipid and protein peroxidation, while peritoneal dialysis (PD) increases protein oxidation [57].

Oxidative stress may not only increase due to the bioincompatible catheters, membranes, and dialysis fluids in HD patients but also due to the low pH and high osmolality of

fluids in peritoneal dialysis patients [28, 36, 37, 58]. In addition, the loss of vitamins and/or trace elements during HD using high-permeable membranes may lead to disruption of the antioxidant system [59].

Another problem is the formation of toxins in the gastrointestinal tract, which worsens the effects of dialysis treatment [60, 61]. Therefore, some authors propose the use of symbiotics that reduce the production and absorption of p-cresol sulfate and indoxyl sulfate [62].

The low, 50% 3-5-year survival rate of dialysis patients may also result from the fact that dialysis is currently mainly focused on urea elimination, although its toxicity is controversial [22, 63]. It seems that using different renal replacement therapies (intermittent hemodialysis or peritoneal dialysis), it is possible to obtain urea and other small particles' clearance comparable to 15% of normal kidney function, and only in the case of home night hemodialysis performed 7 times a week or in renal transplant recipients, urea clearance may reach 50% of normal kidney function. Despite these results, patients with chronic kidney disease, with urea clearance as high as 20-25 ml/min, comparable to patients on dialysis, have fewer clinical signs of uremia. This may be related to a nonproportional clearance of other substances, especially medium molecules [8, 64]. Improved clearance of larger molecules can be achieved with the prolonged duration of treatments [64]. It has been shown that lower concentrations of beta2-microglobulin in dialyzed patients can also be observed in patients with preserved renal residual function, as demonstrated in a study comparing peritoneal dialysis patients with those treated with hemodialysis [65].

**6.1. Hemodialysis.** The purification efficiency for different substances varies depending on the type and parameters of hemodialysis and the class of filtration membranes, which differ in terms of biocompatibility, medium-molecular-weight screening factor, start of molecular weight retention and molecular weight cutoff for dissolved substances with different molecular weight, presence of electric charges and Z potential, thickness, and diffusion coefficient ( $K_d$ ) for different substances [28, 66]. Cuprophan membranes used in the past triggered inflammatory reactions and intensified amyloidosis development [67].

Better biocompatibility of hemodialysis, even compared to hemodiafiltration, can now be achieved by use of dialyzers with vitamin E in low-flow bicarbonate hemodialysis, which reduces inflammation associated with the activity of indoleamine 2,3-dioxygenase 1 and nitric oxide synthesis [68]. Despite the fact that during longer procedures, the clearance for beta2-microglobulin and phosphates is greater, the removal of protein-related toxin has not changed significantly [69, 70].

Standard hemodialysis is the most commonly used renal replacement therapy, which purifies the blood of toxins in the diffusion mechanism, i.e., the passage of <500 Dalton particles from the blood to the dialysis fluid according to the concentration difference [71]. The removal of medium and large particles is impossible during standard hemodialysis, although the use of high-flux membranes during hemo-

dialysis only slightly improves the elimination of medium particles [72].

Another solution is the use of MCO dialysis membranes with medium cutoff values. The clearance of mean particles for these membranes is much higher than for standard membranes used in classical hemodialysis treatments, both low flux HD and high flux HD, and comparable with membranes used in hemodiafiltration [73-75]. Extended hemodialysis using MCO membranes may lead to reduction in mortality comparable to hemodiafiltration treatment, which can be combined with similar efficacy in removing both small, such as urea and creatinine, and medium, such as beta2-microglobulin, particles [73, 75].

The hemodialysis procedure can also remove protein-bound toxins, but only from the free fraction, and the effectiveness of this process is only about 30%. On the other hand, the use of MCO filters may lead to moderate hypoalbuminemia, which may improve the removal of protein-bound toxins [17, 76-80].

**6.2. Hemodiafiltration.** In contrast to the diffusion mechanism, in which substances pass through the membrane at different speeds depending on the blood flow and dialysis fluid, the type of dialysis membrane, and the size of toxins, the convection mechanism, i.e., removal of toxins together with the solvent through the highly permeable membrane, prevails in hemofiltration and not so much in hemodiafiltration. The implementation of such a method allows to purify the body form substances of different sizes, even middle molecules, and their removal is directly proportional to their concentration in plasma. Unfortunately, it requires a return administration of ultrapure fluids, which can be administered both before and after the filter (Figure 2).

Hemodiafiltration is more expensive than hemodialysis because it involves better membrane biocompatibility and the use of ultrapure dialysate. Hemodiafiltration better than hemodialysis removes uremic toxins, both small and medium, because diffusion and convection are responsible for removing the toxins (Figure 2). Hemodiafiltration, compared to hemodialysis, improves parathormone clearance and proinflammatory cytokines (e.g., IL-6, IL-8, and IL-12) and reduces the concentration of  $\beta$ 2-microglobulin, ADMA, SDMA, and appetite suppressants such as leptin, cholecystokinin, tryptophan, and albumin [81, 82]. Patients treated with HDF also have better clearance of homocysteine, guanidine, and polyamines, which reduce nitric oxide production and promote AGE formation. Therefore, patients treated with HDF have lower inflammation and cardiovascular risk [83]. The removal of p-CS during hemodiafiltration may, according to some authors, be comparable to the use of low-flux hemodialysis and high-flux hemodialysis, which emphasizes the low importance of convection in the removal of these dissolved substances [84]. The removal of medium-sized toxins is slightly greater because convection is responsible for the removal of medium-sized toxins during HDF. However, Gomólka et al. [85] found that there are no major differences in the serum clearance of IS and p-CS depending on the dialysis modality (low-flux hemodialysis, high-flux hemodialysis, and postdilution hemodiafiltration). They concluded that

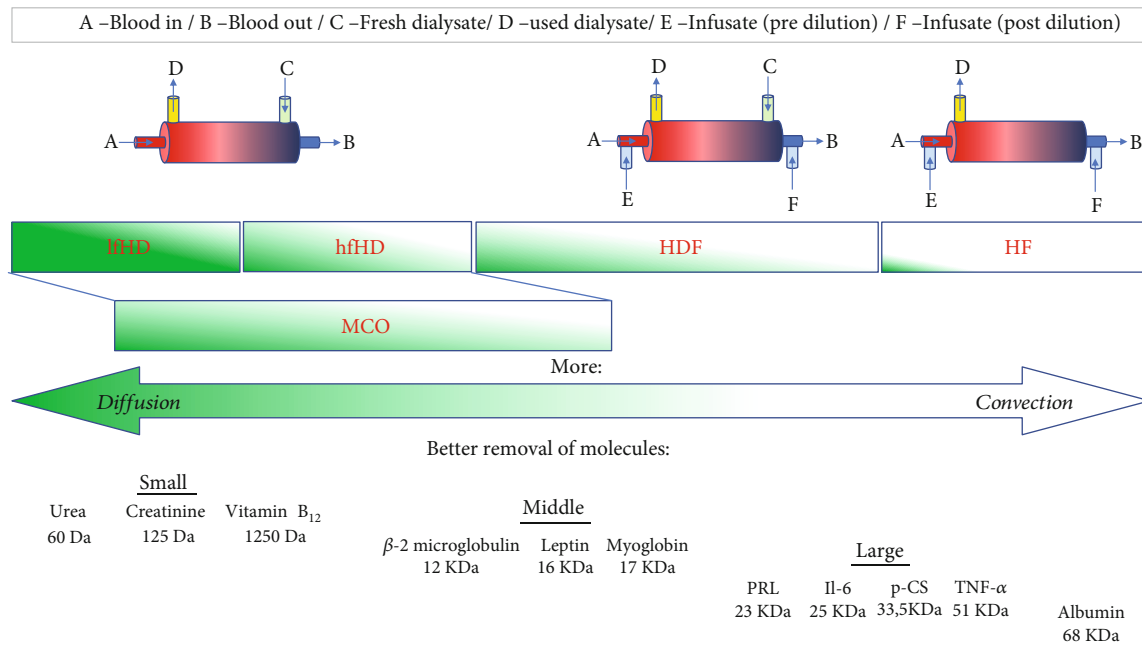


FIGURE 2: Uremic toxin removal by different modalities.

these protein-bound toxins were significantly cleared from the serum already during the first dialysis session, but their level tended to revert during weeks' long dialysis sessions.

Moreover, the method of plasma fluid replenishment is also important—postdilution is more effective than predilution [86–90], and mixed, pre-, and postdilution supplementation is the most effective in purification [91–94]. It has been noted that in people treated with hemodiafiltration, there is less risk of amyloidosis and carpal tunnel syndrome episodes, and that with large exchange volumes, purification is more efficient, which may further reduce mortality from general and cardiovascular causes [95–100].

Studies comparing different types of renal replacement therapy have shown that hemofiltration reduces mortality among patients undergoing renal replacement therapy. The clearance of small and medium molecules during online hemofiltration is similar to that of extended hemodialysis, but may be higher for larger medium molecules [101]. Therefore, the use of hemofiltration improves the removal of medium molecules, including beta2-microglobulin, compared to classical hemodialysis, but also with peritoneal dialysis [90, 102].

## 7. Summary

Elimination of the waste products and toxins generated from a variety of metabolic processes is one of the major kidney functions [103]. Efficient elimination of these solutes is provided by normal kidney function; thus, their blood and tissue concentrations are kept at relatively low levels. On the contrary, these toxin retentions appear to be a major contributor to the development of uremia in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) [104]. In addition, progression of CKD contributes

to the oxidative stress produced by intracellular uremic toxins, leading to inflammation and tissue destruction [105]. Uremic toxins, found in high concentrations in the circulation in patients with ESRD, play an important role in endothelial dysfunction/damage, which in turn contributes to the pathogenesis of cardiovascular diseases, such as atherosclerosis and thrombotic events [106–110]. In CKD, and in particular in dialyzed population, endothelial dysfunction and atherosclerosis are almost universal, as well as cardiovascular complications. Lindner et al. [111] were the first to draw attention to the excessive incidence of atherosclerotic cardiovascular mortality in hemodialyzed patients. Implications of uremic toxins and oxidative stress to atherosclerosis were recently presented in the elegant review by Wojtaszek et al. [112]. Hypoalbuminemia is a frequent finding in CKD, and multiple factors may be contributory, including inflammation, malnutrition, and dialytic losses [113]. Structure of albumin as well as uremia-induced changes in the albumin concentration also may influence protein-bound uremic toxins binding from both a quantitative and qualitative perspective. It was demonstrated that protein-bound compounds, including drugs and endogenous toxins, are secreted by renal proximal tubule cells [114, 115]. Unbound solutes (drugs, uremic toxins, etc.) are transported by specific organic anion transporters; thus, the equilibrium established between bound and unbound solute forms is critical. On the one hand, dialysis increases the state of oxidative stress, and the involved mechanisms include use of bioincompatible membranes and fluids and contamination of dialysate with bacterial endotoxins and occult infections [116–118]. On the other hand, renal replacement therapy, in particular hemodiafiltration, by lower concentration of uremic toxins diminishes oxidative stress leading to reduced cardiovascular and thromboembolic risk. Moreover, successful kidney

transplantation leads not only to the at least partial restoration of kidney function with amelioration of metabolic abnormalities but also to the significant improvement in OS-related markers. Sufficient graft function seems to be a key factor in the restoration to near normal levels of OS biomarkers.

At this moment, despite the increasing number of recognized toxins and their mechanisms of action, it is impossible to determine which of them are the most important and which cause the greatest complications. According to many authors, further studies are needed to assess the clinical consequences of different types of renal replacement therapy as so far large prospective trials have not addressed the effect of various renal replacement modalities on uremic toxin removal with respect to patient outcomes.

## Abbreviations

ADMA:	Asymmetric dimethylarginine
AGEs:	Advanced glycation end products
CKD:	Chronic kidney disease
CRP:	C-reactive protein
CVD:	Cardiovascular disease
eGFR:	Estimated glomerular filtration rate
ESRD:	End-stage renal disease
HD:	Hemodialysis
HDF:	Hemodiafiltration
HOCl:	Hypochlorous acid
ICAM-1:	Intercellular adhesion molecule-1
IL-1:	Interleukin 1
IL-2:	Interleukin 2
IL-4:	Interleukin 4
IL-5:	Interleukin 5
IL-6:	Interleukin 6
IL-8:	Interleukin 8
IL-12:	Interleukin 12
IL-13:	Interleukin 13
IL-18:	Interleukin 18
IS:	Indoxyl sulfate
$K_o$ :	Diffusion coefficient
MCO:	Medium cutoff
NADPH:	Nicotinamide adenine dinucleotide phosphate
NF- $\kappa$ B:	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO:	Nitric oxide
$O_2$ :	Superoxides
ONOO:	Peroxynitrite
PAI-1:	Inhibitor of tissue plasminogen activator
p-CS:	p-Cresyl sulfate
PD:	Peritoneal dialysis
ROS:	Reactive oxygen species
SDMA:	Symmetric dimethylarginine
SOD:	Superoxide dismutase
TGF $\beta$ 1:	Transforming growth factor $\beta$ 1
TFPI:	Tissue factor pathway inhibitor
TNF- $\alpha$ :	Tumor necrosis factor- $\alpha$
t-PA:	Tissue plasminogen activator
VCAM-1:	Vascular adhesion molecule-1
vWF:	von Willebrand factor.

## Conflicts of Interest

There is no conflict of interests to disclose.

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