Online hemodiafiltration (HDF) versus high-flux hemodialysis (hf-HD): A review

Hemodiafiltração online (HDF) versus hemodiálise de alto fluxo (hf-HD): Uma revisão

Hemodiafiltración en línea (HDF) versus hemodiálisis de alto flujo (hf-HD): Una revisión

Andressa Flores Santos
ORCID: https://orcid.org/0000-0001-6496-4333
Federal University of Paraná, Brazil
E-mail: andressaflores@ufpr.br
Regiane Stafim da Cunha
ORCID: https://orcid.org/0000-0002-7925-7698
Federal University of Paraná, Brazil
E-mail: regidacunha@gmail.com
Andrea Emilia Marques Stinghen
ORCID: https://orcid.org/0000-0001-8595-5321
Federal University of Paraná, Brazil
E-mail: andreastinghen@ufpr.br
Wesley Maurício de Souza
ORCID: https://orcid.org/0000-0001-7918-7936
Federal University of Paraná, Brazil
E-mail: wesleysouza@ufpr.br

Abstract
Chronic kidney disease affects a vast part of the world population and as a consequence gradually declines renal function. Patients enter the end stage of kidney disease as the disease progresses, and the use of renal replacement therapy such as hemodialysis then becomes necessary. With the advance of technology, new modalities of dialyzers have been made available in the market with the objective of making the hemodialysis process more efficient and of increasing its biocompatibility. This review aims to discuss different hemodialysis techniques, focusing on online hemodiafiltration and high-flux hemodialysis, in terms of molecular clearance, biocompatibility, cardiovascular stability, survival, safety, and costs. In comparison to conventional hemodialysis (low-flux), online hemodiafiltration and high-flux hemodialysis present a greater capacity to filtrate medium molecular weight molecules, presenting greater biocompatibility and maintaining cardiovascular stability during dialysis sessions, and constituting factors which can justify better outcomes of patients submitted to these modalities. However, studies differ on the real superiority of online hemodiafiltration when compared to high-flux hemodialysis, which highlights the need for further discussion on the subject.
Keywords: Biocompatible materials; Cardiovascular diseases; Renal dialysis; Hemodiafiltration.

Resumo
A doença renal crônica afeta uma vasta parte da população mundial e, como consequência, diminui gradualmente a função renal. Os doentes entram na fase final da doença renal a medida que a doença progride, e o uso de terapia de substituição renal, como a hemodiálise, torna-se necessário. Com o avanço da tecnologia, novas modalidades de dialisadores foram disponibilizadas no mercado com o objetivo de tornar o processo de hemodiálise mais eficiente e de aumentar a sua biocompatibilidade. Esta revisão visa discutir diferentes técnicas de hemodiálise, centrando-se na hemodiafiltração em linha e hemodiálise de alto fluxo, em termos de depuração molecular, biocompatibilidade, estabilidade cardiovascular, sobrevivência, segurança e custos. Em comparação com a hemodiálise convencional (baixo fluxo), a hemodiafiltração em linha e a hemodiálise de alto fluxo apresentam uma maior capacidade de filtrar moléculas de peso molecular médio, apresentando maior biocompatibilidade e mantendo a estabilidade cardiovascular durante as sessões de diálise, constituindo fatores que podem justificar melhores resultados nos pacientes submetidos a estas modalidades. Contudo, os estudos diferem sobre a real superioridade da hemodiafiltração em linha quando comparados com a hemodiálise de alto fluxo, o que evidência a necessidade de uma discussão mais aprofundada sobre o assunto.
Palavras-chave: Materiais biocompatíveis; Doenças cardiovasculares; Diálise renal; Hemodiafiltração.

Resumen
La enfermedad renal crónica afecta a una gran parte de la población mundial y, como consecuencia, disminuye gradualmente la función renal. Los pacientes entran en la fase final de la enfermedad renal a medida que ésta progresa, y entonces se hace necesario el uso de la terapia de sustitución renal, como la hemodiálisis. Con el avance

de la tecnología, se han puesto a disposición del mercado nuevas modalidades de dializadores con el objetivo de hacer más eficiente el proceso de hemodiálisis y de aumentar su biocompatibilidad. Esta revisión pretende discutir las diferentes técnicas de hemodiálisis, centrándose en la hemodiafiltración en línea y la hemodiálisis de alto flujo, en términos de aclaramiento molecular, biocompatibilidad, estabilidad cardiovascular, supervivencia, seguridad y costes. En comparación con la hemodiálisis convencional (de bajo flujo), la hemodiafiltración en línea y la hemodiálisis de alto flujo presentan una mayor capacidad de filtrar moléculas de peso molecular medio, presentando una mayor biocompatibilidad y manteniendo la estabilidad cardiovascular durante las sesiones de diálisis, y constituyendo factores que pueden justificar mejores resultados de los pacientes sometidos a estas modalidades. Sin embargo, los estudios difieren en cuanto a la real superioridad de la hemodiafiltración en línea en comparación con la hemodiálisis de alto flujo, lo que pone de manifiesto la necesidad de seguir discutiendo el tema.

Palabras clave: Materiales biocompatibles; Enfermedades cardiovasculares; Diálisis renal; Hemodiafiltración.

1. Introduction

The main function of the kidney is to eliminate toxins generated by the metabolic processes of the body (Clark et al., 2019). Patients with chronic kidney disease (CKD) or who are in end-stage renal disease (ESRD) have this function affected, which leads to accumulation of the aforementioned toxins in the circulatory system, a condition called "uremia" (Clark & Gao, 2002; Franco et al., 2019). An accumulation of these so-called uremic toxins (UTs) in the body generates several deleterious effects in the organism, including malnutrition, anemia, dermal atrophies, dyslipidemia, metabolic acidosis, inflammation, pericarditis, hypertension, heart failure, coagulation disorders, and cardiovascular disease (CVD). CVDs are the leading cause of death in these patients (Go et al., 2004; Vanholder et al., 2005, Vanholder et al., 2008).

Patients in ESRD require renal replacement therapy (RRT) such as dialysis in order to prevent symptoms and to sustain their life (Pecoits-Filho et al., 2019). Despite technological and management advances to improve the quality of life (QoL) of patients in ESRD, it is notable that there is a high incidence of adverse complications such as hospitalization and death in this population, where the mortality rates of patients in ESRD are higher than patients with diabetes, CVD or cancer (Pecoits-Filho et al., 2019; Saran et al., 2017). However, new hemodialysis techniques are being developed, improved and studied in order to improve this scenario. Conventional low-flux hemodialysis (HD) is not highly effective, and patient morbidity and mortality rates are still high (Locatelli et al., 2015). As an alternative, recent controlled trials demonstrate that dialysis techniques which make use of high-flux membranes or that associate diffusion with convection show superiority over conventional hemodialysis in clinical endpoints (Canaud et al., 2020).

Thus, this review aims to discuss the main characteristics and conclusions of the impact of high-flux hemodialysis (hf-HD) and online hemodiafiltration (HDF) techniques on molecular clearance, biocompatibility, cardiovascular stability, survival, safety and cost.

2. Methodology

The present study is a systematic exploratory review (Reyes, 2020) of scientific research and literature reviews conducted between 1999 and 2020, with the aim of discussing different hemodialysis techniques, focusing on online hemodiafiltration and high flux hemodialysis, in terms of molecular clearance, biocompatibility, cardiovascular stability, survival, safety and costs. MEDLINE/PubMed (U.S.A. National Library of Medicine), Web of Science: Science Citation Index (Clarivate Analysis), SciELO and Google Scholar databases were used to search for articles using the following descriptors: Hemodialysis, Hemodiafiltration, High Flux Hemodialysis, Uremic Toxins, Cardiovascular Stability, Filtration Membranes and Biocompatibility. Articles published before the year 1999 and those without the descriptors in the title and/or abstract were excluded, the remaining clinical and review studies were included in the review process (Figure 1).

Figure 1. Flow chart outlining the protocol adopted in this systematic review.
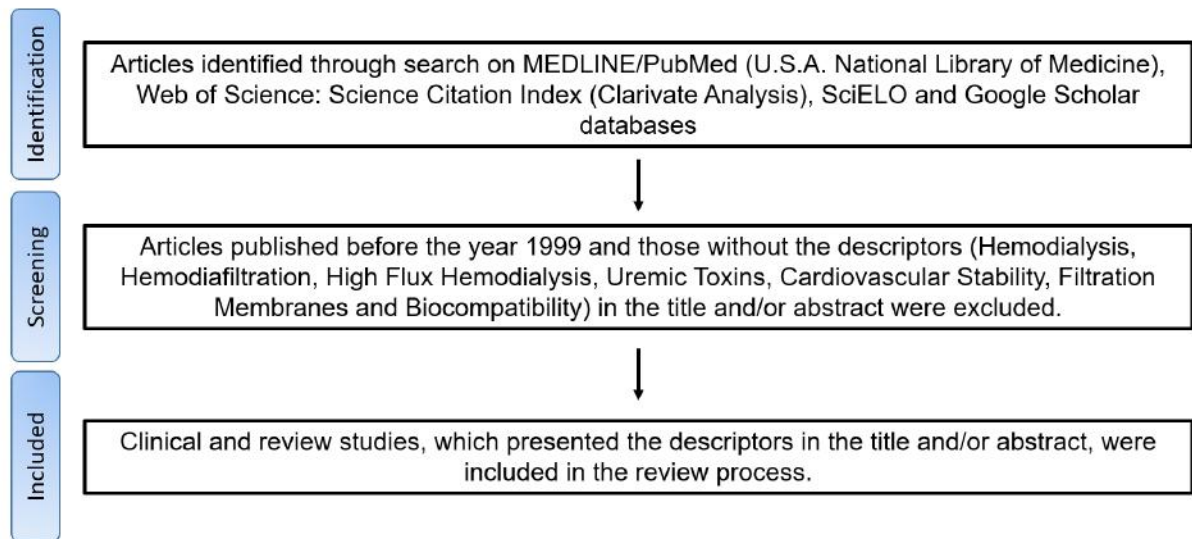
Source: Authors.

3. Hemodialysis Modalities

A suitable method for replacing renal function is HD, which is the most prevalent RRT technique worldwide. New HD modalities have emerged with the advancement in technology, aiming to improve the performance of this technique, as well as to increase the quality of life of patients and reduce the risks associated with the chronic use of RRT (Larkin et al., 2019). Although any RRT type is available in most countries, it is limited to specific subgroups of the population and frequently the most vulnerable populations have no access to treatments nor to diagnostics.

3.1 High-flux hemodialysis (hf-HD)

HD is used to artificially remove circulating toxins by an external filter which contains a semipermeable membrane (Donadio et al., 2017; Vadakedath & Kandi, 2017) with a thickness of about 20 to 45 μm, length of 160 to 250 mm (Sakai, 2000), and pore size ranging from 1 to 14 nm. This dialysis modality (low-flux) mainly targets the filtration of low molecular weight UT (<500 Daltons), which limits its efficiency (Locatelli et al., 2010; Suchy-Dicey et al., 2016) since it makes use of diffusion (Ledebo, 1999; Ledebo & Blankestijn, 2010). The diffusive transport process requires the dialysis fluid, which flows through the counter-current from the dialyzer to blood (Figure 2) (Ledebo, 1999; Ledebo & Blankestijn, 2010; Thomas & Jaber, 2009). The difference in solute concentration between the blood and the dialysate serves as a driving force for diffusive transport, and this force differs for each solute, the diffusion rate is defined by the molecular weight of the solute and its resistance to flow, this resistance is due to the hemodialysis membrane and its physical characteristics. The diffusion rate is inversely proportional to the cubic root of the molecular weight, which favors the clearance of low molecular weight molecules (Ingrid Ledebo & Blankestijn, 2010; Ledebo, 1999).

Alternatively, hf-HD aims to improve the clearance capacity using membranes with larger pores, high ultrafiltration and convective therapy, thus also removing medium molecular weight molecules (>500 Daltons and <12.000 Daltons). The convection process resembles the physiological process in the human kidney, whereby plasma is filtered through the glomerulus, which is selectively permeable, and glomerular filtration depends on a relatively low hydrostatic pressure, convection and solvent drag (Thomas & Jaber, 2009). The blood is filtered through a highly permeable biosynthetic membrane, promoting the removal of low and medium molecular weight molecules, which has a higher filtration capacity of

low molecular weight UT (Meyer et al., 2005; Pecoits-Filho et al., 2019; Thomas & Jaber, 2009). In this modality, the total ultrafiltration can exceed the delimited weight loss and the compensation of this loss occurs within the dialyzer by retrofiltration. Convective transport is considerable due to the permeability of the high flux membranes, but cannot be controlled, which is the main difference when compared to online hemodiafiltration (HDF) (Ledebo & Blankestijn, 2010; Petrie et al., 2008). The convective transport volume must exceed 50 mL/min to have a significant impact on the clearance of medium molecular weight molecules, which does not normally occur in hf-HD (Ledebo, 1999; Lornoy et al., 2000).

Figure 2. Flow chart of different forms of hemodialysis (HD). The fluid flows in the hemodiafilter/dialyzer and the administration of the substitution fluid for low-flux HD, high-flux HD, and HDF are demonstrated.
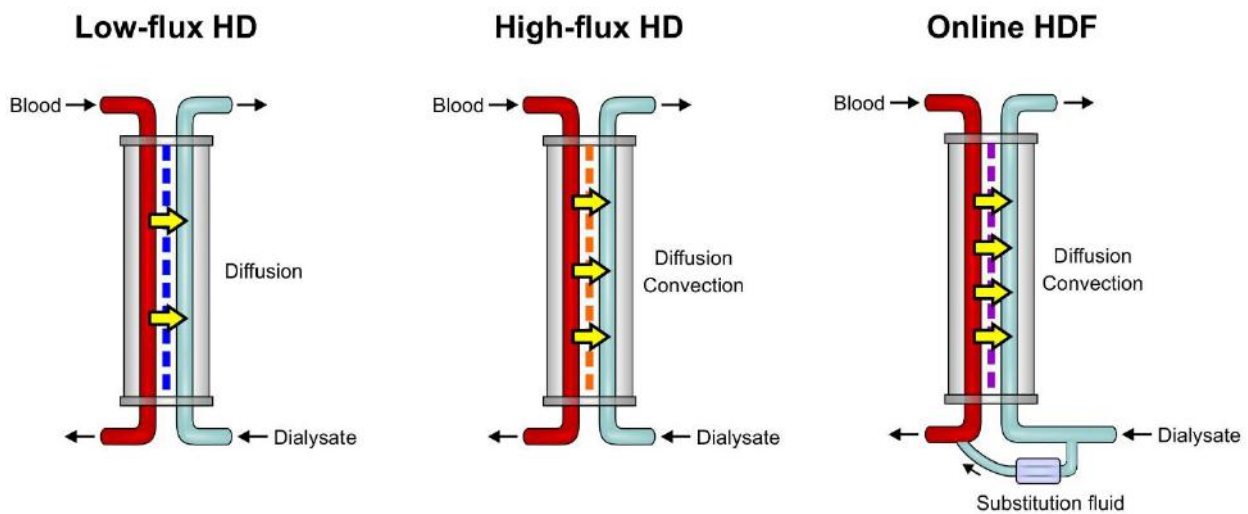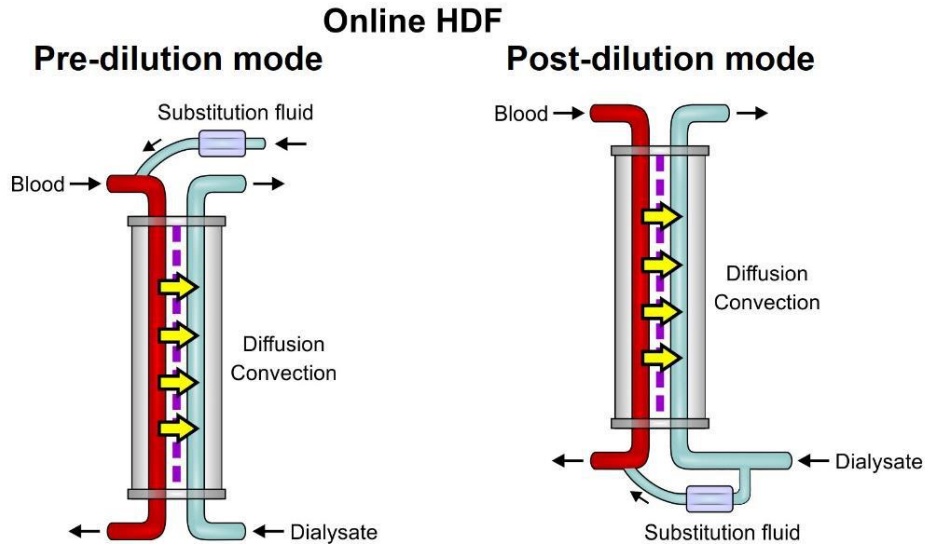

Source: Authors.

In addition, the biocompatibility of high-flux membranes reduces chronic inflammation and oxidative stress, which is strongly associated with malnutrition and atherosclerosis (Pieroni et al., 2015). High-flux dialysis seems to be an efficient alternative compared to other dialysis methods which make use of diffusion and convection, and a satisfactory compromise between efficiency and practicability (Donadio et al., 2017). However, there is no agreement on the equivalence of the techniques (i.e. studies demonstrate the superiority of hemodiafiltration technique when compared to hf-HD (Abad et al., 2016; Locatelli et al., 2018; Peters et al., 2016). Thus, further studies and clarifications on both techniques in terms of molecule clearance and interference in quality of life are necessary.

3.2 Online hemodiafiltration (HDF)

Previously called online haemofiltration was developed with the goal of improving filtration capacity of HD. This modality makes use of diffusion associated with convection and promotes the removal of medium molecular weight molecules, with this being the main advantage when compared to the conventional modality (Pecoits-Filho et al., 2019; Thomas & Jaber, 2009). Weight loss control in this modality is done by infusing a replacement fluid, which has a similar composition to plasma water, and must be sterile and non-pyrogenic. This infusion can be administered before (pre-dilution) or after (post-dilution) the dialysis filter (Figure 3) (Ledebo, 1999; Ledebo & Blankestijn, 2010; Petrie et al., 2008).

Figure 3. Schematic illustration of pre-dilution and post-dilution online hemodiafiltration. The infusion of a replacement fluid can be administered before (pre-dilution mode) or after (post-dilution mode) the dialysis filter. This fluid has a composition similar to plasma water, is sterile and non-pyrogenic.

Source: Authors.

Online hemodiafiltration was first described in the 1970s, however it remains rarely used (Chuasuwan et al., 2020). Several studies have compared HDF to other dialysis methods, however, Donadio et al. (2017) concluded that HDF is a more efficient treatment than low flux hemodialysis, but it is not accessible to all patients. According to Schiffl (2019), only 7% of patients worldwide are treated with HDF, while less than 1% of patients have access to this dialysis technique in the United States, as well as in Latin America.

4. The Clearance of Molecules

Uremic toxin clearance is directly related to kidney functions. The main renal clearance mechanisms are glomerular filtration and tubular secretion, which is characterized by transporter proteins that mediate the influx of uremic toxins through the basolateral membrane and subsequent efflux through the luminal membrane of renal tubule cells, in addition to being responsible for the reabsorption of these solutes (Suchy-Dicey et al., 2016; Wang & Kestenbaum, 2018). However, dialysis techniques in ESRD patients become essential instruments for the removal (at least partially) of uremic toxins from the body (van Gelder et al., 2020; Yamamoto et al., 2016). These compounds are classically divided according to physicochemical properties into three groups: small water-soluble, middle, and protein-bound molecules (Vanholder & Glorieux, 2003).

4.1 Small water-soluble molecules

Small water-soluble molecules are characterized by a molecular size less than 500 Da (Vanholder & Glorieux, 2003). This group includes creatinine (113 Da), urea (60 Da), trimethylamine N-oxide (TMAO; 75 Da), phenylacetylglutamine (264 Da), and guanidine (59 Da), among others (Bain et al., 2006; Poesen et al., 2016). For example, creatinine is mainly cleared by glomerular filtration and is classically used as a marker of kidney function, being part of several formulas for calculating the estimated glomerular filtration rate (eGFR) (Porrini et al., 2019). Creatinine is also cleared by tubular secretion, being a substrate for organic cation transporters (OCT2) and organic anion transporter (OAT2) in the basolateral membrane as well as

multidrug and toxin extrusion (MATE1 and MATE2-K proteins) in the luminal membrane (Ciarimboli et al., 2012; Shen et al., 2015; Tanihara et al., 2007; Urakami et al., 2004). TMAO is another uremic toxin that is associated with decreased renal function and cardiovascular outcomes in patients with CKD (Missailidis et al., 2016; Pelletier et al., 2019; Stubbs et al., 2016). Renal clearance of TMAO is due to glomerular filtration and tubular secretion, in which it is a substrate of OCT1, OCT2, OAT3, and multiple efflux transporters (Gessner et al., 2018; Miyake et al., 2017; Teft et al., 2017; Wu et al., 2017). Small water-soluble molecule removal can occur in dialysis therapies via diffusion in semipermeable membranes. Hai et al. (2015) showed that the reduction rate of TMAO, urea and creatinine after a HD session could reach 86%, 77% and 71%, respectively. In addition, Kim et al. (2019) reported similar removal percentages of small uremic toxins, such as urea, creatinine, uric acid, and phosphate, in the HDF modalities, high-flux dialyzers in HD (hf-HD), and medium cut-off (MCO) dialyzer in hemodialysis (MCO-HD).

4.2 Middle molecules

Middle molecules are mainly composed of peptides larger than 500 Da (Vanholder & Glorieux, 2003). Examples of this group are β2-microglobulin (11,818 Da), interleukin-6 (IL-6; 24,500 Da), complement factor D (26,750 Da), fibroblast growth factor 23 (FGF-23; 32,000 Da), parathyroid hormone (PTH; 9,225 Da), and others. Studies have shown that the type of dialyzer could influence the removal of middle molecular weight uremic toxins (Maduell et al., 2014; Wolley et al., 2018). More recently, MCO dialyzers were developed to obtain optimized permeability, with larger pores which allow the passage of middle molecules (up to about 50 kDa) and minimal albumin loss (Boschetti-De-Fierro et al., 2015; Wolley et al., 2018). Some clinical studies have shown that MCO-HD and HDF is able to more effectively remove middle molecules and a wider range of middle-molecule uremic toxins compared to HF-HD and HD (Belmouaz et al., 2020; Kirsch et al., 2017; Locatelli et al., 2015; Weiner et al., 2020). Belmouaz et al. (2020) demonstrated that MCO-HD had reduction rates of β2-microglobulin and FGF-23 of 73% and 41%, respectively, which is significantly higher than hf-HD. However, the use of MCO membranes in large populations and their possible clinical effects remain to be elucidated.

4.3 Protein-bound molecules

Protein-bound molecules are compounds, usually of small molecular weight, that have high affinity for serum proteins (Vanholder & Glorieux, 2003). The main prototypes of this group are indoxyl sulfate (212 Da), *p*-cresyl sulfate (187 Da), indole-3-acetic acid (175 Da), hippuric acid (179 Da), phenylacetic acid (136 Da), kinurenine (208 Da), 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF; 240 Da), leptin (16,000 Da), and others (Barreto et al., 2009; Liabeuf et al., 2010). The most studied from this group are indoxyl sulfate and *p*-cresyl sulfate, both toxins which accumulate in the body with kidney dysfunction and are associated with mortality in CKD patients (Barreto et al., 2009; Liabeuf et al., 2010). Studies have demonstrated that approximately 90-98% of indoxyl sulfate and *p*-cresyl sulfate non-covalently bind to the Sudlow II binding site of albumin (Devine et al., 2014; Itoh et al., 2012; Smith & Pfaendtner, 2020; Suchy-Dicey et al., 2016). Tubular secretion plays an important role in the renal clearance of protein-bound molecules, in which indoxyl sulfate and *p*-cresyl sulfate are known substrates of OAT1 and OAT3 (Miyamoto et al., 2011; Suchy-Dicey et al., 2016; Wikoff et al., 2011; Wu et al., 2017). However, the removal of these compounds by dialysis therapies is limited due to protein binding capacity. Itoh et al. (2012) demonstrated that the reduction rate of indoxyl sulfate and *p*-cresyl sulfate after a HD session was only 31.8% and 29.1%, respectively. Some studies have shown that molecules (i.e. ibuprofen) are able to displace uremic toxins by competing for the same binding site on albumin, which leads to an increase in the free fraction of these uremic toxins and improve clearance by dialysis therapies (Madero et al., 2019; Shi et al., 2019; Tao et al., 2016). Madero et al. (2019) reported that the ibuprofen infusion into the bloodstream prefilter increased the indoxyl sulfate and *p*-cresyl sulfate concentration in the outflow dialysate

by approximately 2.4-fold in a cohort of 18 hemodialysis patients. Nevertheless, it is necessary to evaluate the use of displacers in relation to other protein-bound uremic toxins, their interaction with albumin and their long-term effect in larger populations (Van Biesen & Eloot, 2019).

5. Biocompatibility of Hemodialysis Membranes

Hemodialysis is a procedure performed in extracorporeal circulation, and the lack of biocompatibility may induce significant clinical and biochemical responses. Due to blood contacting with the components of the hemodialysis circuit, such as dialysis membranes, drains and intravenous fluids administered during the procedure, activation of inflammatory and immune pathways may occur, leading to dialysis-induced oxidative stress and membrane-induced inflammation, which are related to cardiovascular problems (Chang et al., 2014; Gomółka et al., 2020; Ojeda et al., 2020; Claudio Ronco et al., 2018; Claudio Ronco & Clark, 2018). This activation occurs via the alternative pathway of the complementary system, leading to anaphylatoxins being released into the bloodstream, activation of the coagulation cascade and of different cell types (monocytes, neutrophils, basophils, and platelets), and elevating plasma pro-inflammatory cytokine levels such as interleukin-1β (IL-1), IL-6, IL-10, tumor necrosis factor-α (TNF-α) and stimulating the production of proteolytic enzymes by granulocytes (Cohen-Mazor et al., 2014; Gomółka et al., 2020; Ojeda et al., 2020).

Due to the exposure time of the blood to the dialysis membrane surface, the biocompatibility of this HD component is crucial. Membranes have the function of removing water and solutes through various mass separation processes such as diffusion, convection and adsorption (Ojeda et al., 2020; Claudio Ronco & Clark, 2018). These membranes can be traditionally classified according to their composition and permeability, being made of cellulose (modified or unmodified) or synthetic. Unmodified cellulose membranes were the most common in the past, but they were eradicated from the market, and the same has been observed for modified cellulose membranes which have good performance and functionality when compared to synthetic ones; however, their biocompatibility and permeability are limited, preventing their application in convective therapies (Clark et al., 1999; Gomółka et al., 2020; Kalantar-zadeh et al., 2018; Ojeda et al., 2020; Claudio Ronco & Clark, 2018).

These limitations have been surpassed with the advance of biomaterials and with the improvement in the production of fibers that have resulted in new membranes with specific characteristics and refined properties, which have begun to present greater biocompatibility and permeability, in addition to expanding their categorization. Factors such as permeability index, hydrophilic index, adsorption capacity, and electric potential are now considered to define the membrane category (Ronco et al., 2018; Ronco & Clark, 2018). Studies show that the use of synthetic high-flux membranes have greater biocompatibility by reducing chronic inflammation and oxidative stress, as in the case of membranes used in hf-HD and HDF (Clark et al., 1999; Gomółka et al., 2020; Ojeda et al., 2020; Pieroni et al., 2015; Tomo, 2016).

Morena et al. (2019) compared hf-HD and HDF in relation to their biocompatibility and noted no difference between the two methods, with no change in inflammatory parameters (IL-6 and TNF-α) nor in albumin concentration observed in samples from 32 patients submitted to the two dialysis methods and using four different types of hemodialysis membranes. Gomółka et al. (2020) also reaffirmed the adequate biocompatibility of these two dialysis methods by analyzing samples from 19 patients, out of which neutrophil myeloperoxidase (MPO) was not activated during the hemodialysis process and proteolytic enzymes collagenase and cathepsin B showed an alteration in their levels, but normalization occurred after 8 weeks of treatment.

6. Cardiovascular Stability

The most frequent clinical problem in patients during HD is cardiovascular (CV) instability, which occurs due to a decreasing blood volume during filtration, leading to vasoconstriction and reduced perfusion in some body regions, triggering systemic circulatory stress (Locatelli et al., 2018; Penny et al., 2018; Ronco et al., 2000). A patient may experience stunting of the myocardium and of other vital organs or precipitated ischemia as a consequence of this instability (Locatelli et al., 2018; Ok et al., 2013; Penny et al., 2018). Studies point out that it is necessary to accurately monitor possible causes of cardiovascular injuries during HD in order to prevent these cardiovascular events, and provide effective preventive intervention for such injuries (Penny et al., 2018).

Despite studies pointing towards HDF and hf-HD as alternatives to HD to minimize the occurrences of these cardiovascular events, the clinical benefits of HDF compared to hf-HD continue to be debated. Articles highlight both the similarity of the techniques and the superiority of HDF over hf-HD (Table 1) (La Milia et al., 2019; Locatelli et al., 2015, 2018; Shroff et al., 2018). La Milia et al. (2019) stated that the removal of Na^+ balance and plasma tonicity did not differ between hf-HD and HDF and this was not a factor which could explain the superiority of HDF. Studies have evidenced that HDF can improve cardiovascular stability when compared to hf-HD (Locatelli et al., 2018) in patients receiving higher convection volumes, however this limits the reach of this technique, since patients who have suboptimal vascular access or time limitations associated with dialysis may not reach these convection volumes (Grooteman et al., 2012; Ok et al., 2013; J. R. Smith et al., 2017).

Table 1. Clinical studies comparing dialysis modalities.

Reference	Country and years	Study type	N. of patients	Hemodialysis modalities	Objectives	Conclusion
(Morena et al., 2019)	France 2016-2018	Prospective multicenter randomized comparative cross-over trial	32	hf-HD vs post-HDF	Solute clearance and biocompatibility profile	Both dialysis methods were shown to be associated with good removal of the tested uremic toxins and good biocompatibility profiles, with an additional gain in removal performances with HDF.
(Belmouaz et al., 2020)	France 2017-2018	Cross-over prospective study	40	MCO-HD vs hf-HD	Myoglobin reduction ratio, clearance of larger middle molecules and PBUTs, interference in nutrition, inflammation, anemia and oxidative stress	Compared to HF-HD, MCO-HD induces a higher myoglobin reduction ratio, but also reduces the pre-dialysis levels of other medium molecules, including beta2-microglobulin, and kappa and lambda free light chain. Thus, MCO-HD appears as a strategy in the removal of medium-molecular-weight toxins, and can be considered an alternative to HDF.
(van Gelder et al., 2020)	Netherlands 2004-2009	Randomized multicenter-controlled trial	80	HDF	Clearance of PBUTs, mortality and cardiovascular events	HDF did not consistently decrease plasma PBUT concentrations in patients and no relationship was found between PBUTs and cardiovascular endpoints and mortality.
(Kim et al., 2019)	Republic of Korea 2020	Observational prospective study	6	MCO-HD vs hf-HD vs pre-HDF	Clearance of larger middle molecules	MCO-HD showed significantly greater clearance of large medium molecules and achieved better clearance of and kappa and lambda free light chain than hf-HD and HDF, without the need for large convection volumes or high blood flow rates. MCO-HD presents an advantage for older adult patients with vascular access deficiencies and HD patients without access to HDF.
(Kirsch et al., 2017)	Austria and Germany 2015	Prospective, open-label, 4-arm, randomized, active control, crossover pilot study	20	MCO-HD vs hf-HD	Clearance of larger middle molecules	MCO HD removed a wide range of molecules from the medium more effectively than high-flux HD and even exceeds the performance of high-volume HDF for large solutes, particularly kappa free light chain.
(Donadio et al., 2017)	Italy 2017	Randomized cross-over study	30	HD vs hf-HD vs HDF	Safety, efficiency, and removal mechanisms of toxins	The clearance of small toxins was similar between hf-HD and HD. β2-microglobulin was only removed with hf-HD, which had excellent tolerability. The efficiency of hf-HD was similar to HDF. Proteomic analysis demonstrated that only high-flow membranes remove and adsorb small proteins. hf-HD may be an efficient alternative to HDF.
(Locatelli et al., 2018)	Belgium, France, Germany, Italy, Spain, Sweden and United Kingdom 2009-2011 2012-2015	Prospective multicenter randomized trial	8567	HD vs HDF	Mortality	The results do not indicate that HDF provides superior patient survival compared to HD.
(Peters et al., 2016)	Netherlands, Canada, Norway, France and Turkey 2016	Multicenter randomized controlled trial	2973	HD vs HDF	Mortality	HDF reduced the risk of all-cause mortality and cardiovascular mortality.

|						
(Canaud et al., 2006)	European countries 1998-2001	Prospective multicenter trial	2165	Lf-HD vs hf-HD vs low-efficacy HDF vs high-efficacy HDF	Mortality	HDF may improve patient survival regardless of its higher dialysis dose compared to the other modalities tested, but randomized controlled trials are still needed before recommendations can be made for clinical practice.
(Francisco Maduell et al., 2013)	Spain 2013	Multicenter, open-label, randomized controlled trial	21	HD vs HDF	Mortality	HDF reduces all-cause mortality when compared to HD. The leading causes of mortality, cardiovascular and infectious diseases, were significantly reduced. HDF can become the first-line option in hemodialysis patients.
(Ok et al., 2013)	Turkey 2007-2008	Prospective, randomized, controlled trial	782	Hf-HD vs HDF	Mortality and cardiovascular events	There was no difference between HDF and hd-HD with respect to the all-cause mortality rate and the rate of nonfatal cardiovascular events. However, when performing a post-hoc analysis, HDF with high replacement volumes was shown to provide a survival benefit in the study patients.
(Grooteman et al., 2012)	Netherlands, Canada and Norway 2004-2009	Prospective randomized study	714	HD vs HDF	Mortality and cardiovascular events	HDF and HD proved similar with respect to all-cause mortality and cardiovascular events. For patients who received HDF the possibility of a survival benefit is suggested, although this subgroup finding requires confirmation.
(Shroff et al., 2018)	United Kingdom 2014-2019	Non-randomised parallel-arm intervention study	150	HD vs HDF	Growth and cardiovascular outcomes in children	HDF effectively improves outcomes in children when compared to HD, including cardiovascular, anthropometric, nutritional and health-related quality of life measures. Physicians and dialysis commissioners need to consider HDF therapy for children.
(Locatelli et al., 2010)	Italy 2008-2010	Prospective, multicenter randomized study	146	HD vs online predilution hemofiltration (HF) vs pre-HDF	Intradialytic hypotension	Patients who were treated with HDF and HF showed a lower frequency of symptomatic intradialytic hypotension compared to patients who were treated with HD and, without relevant adverse effects. This beneficial effect was more pronounced in HDF, associated with a significant increase in pre-dialysis systolic blood pressure.
(Den Hoedt et al., 2014)	Netherlands, Canada and Norway 2004-2010	Randomized controlled trial	405	Hf-HD vs HDF	Systemic inflammation	Long-term HDF reduces inflammatory activity compared to HD.
(Smith et al., 2017)	United Kingdom 2013-2014	Randomized, Single-Blind, Crossover Trial	100	Hf-HD vs HDF	Recovery Time	Similar post-treatment recovery times and similar health-related quality of life scores for both modalities.
(Leme et al., 2020)	Brazil 2016-2017	Cross-sectional study	176	Hf-HD vs HDF	Vitality and physical activity	The perceived post dialytic patient fatigue showed no association with physical activity.
(Pecoits-Filho et al., 2020)	Brazil 2016-2017	Prospective, multicenter randomized controlled trial	195	Hf-HD vs HDF	Physical activity	Despite HDF achieving a high convective volume and a positive impact on solute removal, it did not improve measured physical activity compared to hf-HD.
(Han et al., 2020)	Brazil 2016-2017	Prospective, multicenter, randomized controlled trial	173	hf-HD vs HDF	Self-reported sleep duration	The two dialysis modalities had no effect on self-reported sleep duration.

Source: Authors.

7. Survival

Renal function impacts the QoL of patients in ERSD and, like the use of RRT, interferes with morbidity and mortality (Perl et al., 2017; Peters et al., 2016). Studies based on cross-sectional and validated measures of health-related QoL among patients undergoing HD show a dramatic reduction in QoL when compared to the general population and to patients with other chronic diseases. Therefore, care of HD patients includes providing adequate nutrition as well as sufficient dialysis, maintaining vascular access, minimizing hospitalizations, and most importantly improving or maintaining their quality of life (Table 1) (Abdelsalam et al., 2020).

The high morbidity and mortality rates in patients undergoing HD have been associated with inadequate rates of the removal of medium molecular weight molecules, which has influenced the implementation of new HD techniques such as hf-HD or HDF and of using new classes of filtration membranes (Morena et al., 2019; Okuno et al., 2009; Peters et al., 2016). Eknoyan et al. (2002) demonstrated that hf-HD significantly impacts survival in the long term, with a 32% reduction in mortality in patients who participated in the study. Other studies also evidence an interference of hf-HD in decreasing the incidence of complications, treatment duration, and in improving survival (Table 1) (Bousquet-Santos et al., 2019; Xue et al., 2020; Zhao et al., 2019).

Studies in the literature on the influence of HDF on patient survival diverge (Locatelli et al., 2018). Articles state that despite providing additional elimination of medium molecular weight toxins compared to HD, HDF is not associated with a lower mortality risk (Peters et al., 2016). However, other clinical studies in dialysis patients have shown benefits of this technique in relation to survival. Peters et al. (2016) noted that patients undergoing HDF had a considerably lower risk of all-cause mortality than those receiving HD, while the risk of long-term CVD mortality in HDF patients was 31% lower than in patients receiving HD. Compared to hf-HD, there is no consensus on the superiority of HDF (Figure 4).

Figure 4. Average and standard deviations of all-cause mortalities related to HD, hf-HD and HDF. From references (Chuasuwan et al., 2020; Ok et al., 2013; Shroff et al., 2018; Den Hoedt et al., 2014, and Villa et al., 2011), HDF to HD ratios were obtained and then converted to HDF to hf-HD ratios based on reference (Ojeda et al., 2020), which compared all-cause mortalities among these 3 dialysis methods.
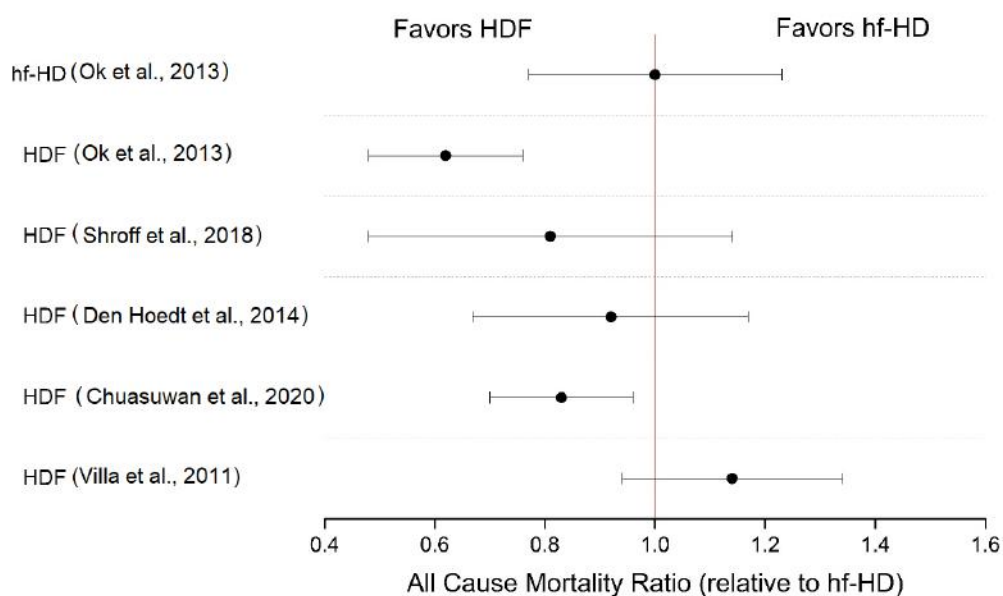
Source: Authors.

8. Safety and Cost

HD is a costly treatment that is essential for ESRD patients (Villa et al., 2011). Safety and costs aspects of implementing HD modalities are relevant and could have an impact on public and private health systems, especially considering the increase in the prevalence and incidence of CKD worldwide (Bikbov et al., 2020; Villa et al., 2011).

Regarding safety, the International Organization for Standardization (ISO) 23500-5:2019 and other regulatory guidelines specify the quality aspects, such as chemical and microbiologic quality standards, for dialysis fluids used in HD, HDF and related therapies (Kawasaki et al., 2009). Historically, failures in the quality control system in dialysis have led to contamination outbreaks, which has diminished over time due to best practices and regulatory standards (Coulliette & Arduino, 2013; Roth & Jarvis, 2000). HDF uses especially large convection volumes and the substitution fluid needs to be sterile and non-pyrogenic as it is infused into the patient, and is therefore important to ensure a safe and effective procedure (Tattersall & Ward, 2013; Ward et al., 2018). Clinical studies have supported the use of HDF, indicating quality and microbiological control (Bolasco et al., 2013; Penne et al., 2009; Vaslaki et al., 2000). Moreover, ultrapure dialysate reduced markers of inflammation and oxidative stress (Susantitaphong et al., 2013).

The cost-effectiveness of low-flux HD, high-flux HD, and HDF modalities is comparatively complex considering the quality-adjusted life year (QALY), various economic aspects, and methodologies used. Lévesque et al. (2015) demonstrated that high efficiency HDF is cost-effective compared to low-flux HD. Takura et al. (2013) also suggest that HDF is cost-effective. Similarly, Ramponi et al. (2016) found that HDF is cost-effective compared to hf-HD, particularly among younger patients. However, Mazairac et al. (2013) reported that HDF cannot be considered a cost-effective modality when compared to HD, even in evaluating costs per QALY.

9. Final Considerations

Hemodialysis has proven to be a viable and important alternative in treating ESRD patients, even with the limitations involved in the initial modalities of renal function replacement. In this review, the definition of hemodialysis, as well as hf-HD and HDF, and their involvement in molecular clearance, cardiovascular stability, and survival were described. Information on biocompatibility of hemodialysis membranes, safety and cost were also discussed. Despite the existence of clinical studies, the superiority of HDF compared to hf-HD is not yet clear, and new clinical studies should be designed in order to clearly prove the benefits of HDF with respect to molecular clearance and mortality.

Acknowledgments

References

Abad, S., Vega, A., Quiroga, B., Arroyo, D., Panizo, N., Reque, J. E., & López-Gómez, J. M. (2016). Protein-bound toxins: Added value in their removal with high convective volumes. *Nefrología*, 36(6), 637–642. https://doi.org/10.1016/j.nefroe.2016.05.011

Abdelsalam, M., Demerdash, T. M., Assem, M., Awais, M., Shaheen, M., Sabri, A., Alanany, H., Kashgary, A., & Alsuwaida, A. (2020). Improvement of clinical outcomes in dialysis: No convincing superiority in dialysis efficacy using hemodiafiltration vs high-flux hemodialysis. *Therapeutic Apheresis and Dialysis*, 25(4), 483-489. https://doi.org/10.1111/1744-9987.13492

Bain, M. A., Faull, R., Fornasini, G., Milne, R. W., & Evans, A. M. (2006). Accumulation of trimethylamine and trimethylamine-N-oxide in end-stage renal disease patients undergoing haemodialysis. *Nephrology Dialysis Transplantation*, 21(5), 1300–1304. https://doi.org/10.1093/ndt/gfk056

Barreto, F. C., Barreto, D. V., Liabeuf, S., Meert, N., Glorieux, G., Temmar, M., Choukroun, G., Vanholder, R., & Massy, Z. A. (2009). Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. *Clinical Journal of the American Society of Nephrology*, 4(10), 1551–1558. https://doi.org/10.2215/CJN.03980609

Belmouaz, M., Bauwens, M., Hauet, T., Bossard, V., Jamet, P., Joly, F., Chikhi, E., Joffrion, S., Gand, E., & Bridoux, F. (2020). Comparison of the removal of uraemic toxins with medium cut-off and high-flux dialysers: A randomized clinical trial. *Nephrology Dialysis Transplantation*, 35(2), 328–335. https://doi.org/10.1093/ndt/gfz189

Bikbov, B., Purcell, C. A., Levey, A. S., Smith, M., Abdoli, A., Abebe, M., Adebayo, O. M., Afarideh, M., Agarwal, S. K., Agudelo-Botero, M., Ahmadian, E., Al-Aly, Z., Alipour, V., Almasi-Hashiani, A., Al-Raddadi, R. M., Alvis-Guzman, N., Amini, S., Andrei, T., Andrei, C. L., &Murray, C. J. L. (2020). Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, 395(10225), 709–733. https://doi.org/10.1016/S0140-6736(20)30045-3

Bolasco, P., Contu, A., Meloni, P., Vacca, D., & Murtas, S. (2013). The evolution of technological strategies in the prevention of dialysis water pollution: Sixteen years' experience. *Blood Purification*, 34(3–4), 238–245. https://doi.org/10.1159/000343127

Boschetti-De-Fierro, A., Voigt, M., Storr, M., & Krause, B. (2015). MCO Membranes: Enhanced Selectivity in High-Flux Class. *Scientific Reports*, 5, 1–7. https://doi.org/10.1038/srep18448

Bousquet-Santos, K., Da Costa, L. da G., & Andrade, J. M. D. L. (2019). Nutritional status of individuals with chronic renal failure in hemodialysis in the Unified Health System. *Ciência e Saúde Coletiva*, 24(3), 1189–1199. https://doi.org/10.1590/1413-81232018243.11192017

Canaud, B., Bragg-Gresham, J. L., Marshall, M. R., Desmeules, S., Gillespie, B. W., Depner, T., Klassen, P., & Port, F. K. (2006). Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney International*, 69(11), 2087–2093. https://doi.org/10.1038/sj.ki.5000447

Canaud, B., Köhler, K., Sichart, J. M., & Möller, S. (2020). Global prevalent use, trends and practices in haemodiafiltration. *Nephrology Dialysis Transplantation*, 35(3), 398–407. https://doi.org/10.1093/ndt/gfz005

Chang, T., Define, L., Alexander, T., & Kyu, T. (2014). *In vitro* investigation of antioxidant, anti-inflammatory, and antiplatelet adhesion properties of genistein-modified poly (ethersulfone)/ poly (vinylpyrrolidone) hemodialysis membranes. *Journal of Biomedical Materials Research Part B Applied Bioamterials*, 539-547. https://doi.org/10.1002/jbm.b.33215

Chuasuwan, A., Chuasuwan, A., Pooripussarakul, S., Thakkinstian, A., Ingsathit, A., Ingsathit, A., & Pattanaprateep, O. (2020). Comparisons of quality of life between patients underwent peritoneal dialysis and hemodialysis: A systematic review and meta-analysis. *Health and Quality of Life Outcomes*, 18(1), 1–11. https://doi.org/10.1186/s12955-020-01449-2

Ciarimboli, G., Lancaster, C. S., Schlatter, E., Franke, R. M., Sprowl, J. A., Pavenstädt, H., Massmann, V., Guckel, D., Mathijssen, R. H. J., Yang, W., Pui, C. H., Relling, M. V., Herrmann, E., & Sparreboom, A. (2012). Proximal tubular secretion of creatinine by organic cation transporter OCT2 in cancer patients. *Clinical Cancer Research*, 18(4), 1101–1108. https://doi.org/10.1158/1078-0432.CCR-11-2503

Clark, W. R. C., Amburger, R. J. H., Ysaght, M. J. L., Division, R., Corporation, B. H., Park, M., & Division, N. (1999). Effect of membrane composition and structure on solute removal and biocompatibility in hemodialysis. *Kidney International*, 56(6), 2005–2015.

Clark, W. R., Dehghani, N. L., Narsimhan, V., & Ronco, C. (2019). Uremic Toxins and their Relation to Dialysis Efficacy. *Blood Purification*, 48(4), 299–314. https://doi.org/10.1159/000502331

Clark, W. R., & Gao, D. (2002). Determinants of uraemic toxin removal. *Nephrology Dialysis Transplantation*, 17(SUPPL. 3), 30–34. https://doi.org/10.1093/ndt/17.suppl_3.30

Cohen-Mazor, M., Mazor, R., Kristal, B., & Sela, S. (2014). Elastase and cathepsin G from primed leukocytes cleave vascular endothelial cadherin in hemodialysis patients. *BioMed Research International*, 2014, 10 pages. https://doi.org/10.1155/2014/459640

Coulliette, A. D., & Arduino, M. J. (2013). Hemodialysis and water quality. *Seminars in Dialysis*, 26(4), 427–438. https://doi.org/10.1111/sdi.12113

Den Hoedt, C. H., Bots, M. L., Grooteman, M. P. C., Van Der Weerd, N. C., Mazairac, A. H. A., Penne, E. L., Levesque, R., Ter Wee, P. M., Nubé, M. J., Blankestijn, P. J., & Van Den Dorpel, M. A. (2014). Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. *Kidney International*, 86(2), 423–432. https://doi.org/10.1038/ki.2014.9

Devine, E., Krieter, D. H., Rüth, M., Jankovski, J., & Lemke, H. D. (2014). Binding affinity and capacity for the uremic toxin indoxyl sulfate. *Toxins*, 6(2), 416–430. https://doi.org/10.3390/toxins6020416

Donadio, C., Kanaki, A., Sami, N., & Tognotti, D. (2017). High-Flux Dialysis: Clinical, Biochemical, and Proteomic Comparison with Low-Flux Dialysis and On-Line Hemodiafiltration. *Blood Purification*, 44(2), 129–139. https://doi.org/10.1159/000476053

Eknoyan, G., Beck, G. J., Cheung, A. K., Daugirdas, J. T., Greene, T., Kusek, J. W., Allon, M., Bailey, J., Delmez, J. A., Depner, T. A., Dwyer, J. T., Levey, A. S. & et al. (2002). Effect of dialysis and membrane flux in Maintenance Hemodialysis. *The New England Journal of Medicine*, 347(25), 2010–2019.

Franco, A. O., Starosta, R. T., & Roriz-Cruz, M. (2019). The specific impact of uremic toxins upon cognitive domains: a review. *Jornal Brasileiro de Nefrologia*, 41(1), 103–111. https://doi.org/10.1590/2175-8239-JBN-2018-0033

Gessner, A., König, J., & Fromm, M. F. (2018). Contribution of multidrug and toxin extrusion protein 1 (MATE1) to renal secretion of trimethylamine-N-oxide (TMAO). *Scientific Reports*, 8(1), 22–24. https://doi.org/10.1038/s41598-018-25139-8

Go, A. S., Chertow, G. M., Fan, D., McCulloch, C. E., & Hsu, C. (2004). Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *New England Journal of Medicine*, 351(13), 1296–1305. https://doi.org/10.1056/nejmoa041031

Gomółka, M., Niemczyk, L., Szamotulska, K., Mossakowska, M., Smoszna, J., Rymarz, A., Pączek, L., & Niemczyk, S. (2020). Biocompatibility of Hemodialysis. *Advances in Experimental Medicine and Biology*, 1251, 91–97. https://doi.org/10.1007/5584_2019_461

Grooteman, M. P. C., Van Den Dorpel, M. A., Bots, M. L., Penne, E. L., Van Der Weerd, N. C., Mazairac, A. H. A., Den Hoedt, C. H., Van Der Tweel, I., Lévesque, R., Nubé, M. J., Ter Wee, P. M., & Blankestijn, P. J. (2012). Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *Journal of the American Society of Nephrology*, 23(6), 1087–1096. https://doi.org/10.1681/ASN.2011121140

Hai, X., Landeras, V., Dobre, M. A., DeOreo, P., Meyer, T. W., & Hostetter, T. H. (2015). Mechanism of prominent trimethylamine oxide (TMAO) accumulation in hemodialysis patients. *PLoS ONE*, 10(12), 1–7. https://doi.org/10.1371/journal.pone.0143731

Han, M., Guedes, M., Larkin, J., Raimann, J. G., Lesqueves Barra, A. B., Canziani, M. E. F., Cuvello Neto, A. L., Poli-De-Figueiredo, C. E., Kotanko, P., & Pecoits-Filho, R. (2020). Effect of Hemodiafiltration on Self-Reported Sleep Duration: Results from a Randomized Controlled Trial. *Blood Purification*, 49(1–2), 168–177. https://doi.org/10.1159/000504242

Itoh, Y., Ezawa, A., Kikuchi, K., Tsuruta, Y., & Niwa, T. (2012). Protein-bound uremic toxins in hemodialysis patients measured by liquid chromatography/tandem mass spectrometry and their effects on endothelial ROS production. *Analytical and Bioanalytical Chemistry*, 403(7), 1841–1850. https://doi.org/10.1007/s00216-012-5929-3

Kalantar-zadeh, K., Block, G., Mcallister, C. J., Humphreys, M. H., Kopple, J. D., & Al, K. E. T. (2018). Appetite and inflammation , nutrition , anemia , and clinical outcome in hemodialysis in patients. *The American Journal of Clinical Nutrition*, 80(2), 299–307.

Kawasaki, T., Uchino, J., Shinoda, T., & Kawanishi, H. (2009). Guidance of technical management of dialysis water and dialysis fluid for the Japan association for clinical engineering technologists. *Blood Purification*, 27(SUPPL. 1), 41–49. https://doi.org/10.1159/000213497

Kim, T. H., Kim, S. H., Kim, T. Y., Park, H. Y., Jung, K. S., Lee, M. H., Jhee, J. H., Lee, J. E., Choi, H. Y., & Park, H. C. (2019). Removal of large middle molecules via haemodialysis with medium cut-off membranes at lower blood flow rates: An observational prospective study. *BMC Nephrology*, 21(1), 1–9. https://doi.org/10.1186/s12882-019-1669-3

Kirsch, A. H., Lyko, R., Nilsson, L. G., Beck, W., Amdahl, M., Lechner, P., Schneider, A., Wanner, C., Rosenkranz, A. R., & Krieter, D. H. (2017). Performance of hemodialysis with novel medium cut-off dialyzers. *Nephrology Dialysis Transplantation*, 32(1), 165–172. https://doi.org/10.1093/ndt/gfw310

La Milia, V., Ravasi, C., Carfagna, F., Alberghini, E., Baragetti, I., Buzzi, L., Ferrario, F., Furiani, S., Barbone, G. S., & Pontoriero, G. (2019). Sodium removal and plasma tonicity balance are not different in hemodialysis and hemodiafiltration using high-flux membranes. *Journal of Nephrology*, 32(3), 461–469. https://doi.org/10.1007/s40620-018-00581-z

Larkin, J. W., Han, M., Han, H., Guedes, M. H., Gonçalves, P. B., Poli-de-Figueiredo, C. E., Cuvello-Neto, A. L., Barra, A. B. L., Moraes, T. P., Usvyat, L. A., Kotanko, P., Canziani, M. E. F., Raimann, J. G., Pecoits-Filho, R., & For the HDFIT Study Investigators (2019). Impact of Hemodialysis and Post-Dialysis Period on Granular Activity Levels. BMC Nephrology, 21, 197-214. https://doi.org/10.21203/rs.2.16392/v1

Ledebo, I. (1999). On-line hemodiafiltration: Technique and therapy. *Advances in Renal Replacement Therapy*, 6(2), 195–208. https://doi.org/10.1016/S1073-4449(99)70038-5

Ingrid, L., & Blankestijn, P. J. (2010). Haemodiafiltration - Optimal efficiency and safety. *NDT Plus*, 3(1), 8–16. https://doi.org/10.1093/ndtplus/sfp149

Leme, J., Guedes, M., Larkin, J., Han, M., Barra, A. B. L., Canziani, M. E. F., Cuvello Neto, A. L., Poli-de-Figueiredo, C. E., de Moraes, T. P., & Pecoits-Filho, R. (2020). Patient perception of vitality and measured physical activity in patients receiving haemodialysis. *Nephrology*, 25(11), 865–871. https://doi.org/10.1111/nep.13758

Lévesque, R., Marcelli, D., Cardinal, H., Caron, M. L., Grooteman, M. P. C., Bots, M. L., Blankestijn, P. J., Nubé, M. J., Grassmann, A., Canaud, B., & Gandjour, A. (2015). Cost-Effectiveness Analysis of High-Efficiency Hemodiafiltration Versus Low-Flux Hemodialysis Based on the Canadian Arm of the CONTRAST Study. *Applied Health Economics and Health Policy*, 13(6), 647–659. https://doi.org/10.1007/s40258-015-0179-0

Liabeuf, S., Barreto, D. V., Barreto, F. C., Meert, N., Glorieux, G., Schepers, E., Temmar, M., Choukroun, G., Vanholder, R., & Massy, Z. A. (2010). Free *p*-cresylsulphate is a predictor of mortality in patients at different stages of chronic kidney disease. *Nephrology Dialysis Transplantation*, 25(4), 1183–1191. https://doi.org/10.1093/ndt/gfp592

Locatelli, F., Altieri, P., Andrulli, S., Bolasco, P., Sau, G., Pedrini, L. A., Basile, C., David, S., Feriani, M., Montagna, G., Di Iorio, B. R., Memoli, B., Cravero, R., Battaglia, G., & Zoccali, C. (2010). Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. *Journal of the American Society of Nephrology*, 21(10), 1798–1807. https://doi.org/10.1681/ASN.2010030280

Locatelli, F., Karaboyas, A., Pisoni, R. L., Robinson, B. M., Fort, J., Vanholder, R., Rayner, H. C., Kleophas, W., Jacobson, S. H., Combe, C., Port, F. K., & Tentori, F. (2018). Mortality risk in patients on hemodiafiltration versus hemodialysis: A "real-world" comparison from the DOPPS. *Nephrology Dialysis Transplantation*, 33(4), 683–689. https://doi.org/10.1093/ndt/gfx277

Locatelli, F., Violo, L., Longhi, S., & Del Vecchio, L. (2015). Current Evidence in Haemodiafiltration. *Blood Purification*, 40(SUPPL 1), 24–29. https://doi.org/10.1159/000437410

Lornoy, W., Becaus, I., Billiouw, J. M., Sierens, L., Van Malderen, P., & D'Haenens, P. (2000). On-line haemodiafiltration. Remarkable removal of β2-microglobulin. Long-term clinical observations. *Nephrology Dialysis Transplantation*, 15(SUPPL. 1), 49–54. https://doi.org/10.1093/oxfordjournals.ndt.a027964

Madero, M., Cano, K. B., Campos, I., Tao, X., Maheshwari, V., Brown, J., Cornejo, B., Handelman, G., Thijssen, S., & Kotanko, P. (2019). Removal of protein-bound uremic toxins during hemodialysis using a binding competitor. *Clinical Journal of the American Society of Nephrology*, 14(3), 394–402. https://doi.org/10.2215/CJN.05240418

Maduell, F., Arias-Guillen, M., Fontseré, N., Ojeda, R., Rico, N., Vera, M., Elena, M., Bedini, J. L., Wieneke, P., & Campistol, J. M. (2014). Elimination of large uremic toxins by a dialyzer specifically designed for high-volume convective therapies. *Blood Purification*, 37(2), 125–130. https://doi.org/10.1159/000358214

Maduell, F., Moreso, F., Pons, M., Ramos, R., Mora-Macià, J., Carreras, J., Soler, J., Torres, F., Campistol, J. M., & Martinez-Castelao, A. (2013). High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *Journal of the American Society of Nephrology*, 24(3), 487–497. https://doi.org/10.1681/ASN.2012080875

Mazairac, A. H. A., Blankestijn, P. J., Grooteman, M. P. C., Lars Penne, E., Van Der Weerd, N. C., Den Hoedt, C. H., Buskens, E., Van Den Dorpel, M. A., Ter Wee, P. M., Nubé, M. J., Bots, M. L., & Ardine De Wit, G. (2013). The cost-utility of haemodiafiltration versus haemodialysis in the convective transport study. *Nephrology Dialysis Transplantation*, 28(7), 1865–1873. https://doi.org/10.1093/ndt/gft045

Meyer, T. W., Walther, J. L., Pagtalunan, M. E., Martinez, A. W., Torkamani, A., Fong, P. D., Recht, N. S., Robertson, C., & Hostetter, T. H. (2005). The clearance of protein-bound solutes by hemofiltration and hemodiafiltration. *Kidney International*, 68(2), 867–877. https://doi.org/10.1111/j.1523-1755.2005.00469.x

Missailidis, C., Hällqvist, J., Qureshi, A. R., Barany, P., Heimbürger, O., Lindholm, B., Stenvinkel, P., & Bergman, P. (2016). Serum trimethylamine-N-Oxide is strongly related to renal function and predicts outcome in chronic kidney disease. *PLoS ONE*, 11(1), 1–14. https://doi.org/10.1371/journal.pone.0141738

Miyake, T., Mizuno, T., Mochizuki, T., Kimura, M., Matsuki, S., Irie, S., Ieiri, I., Maeda, K., & Kusuhara, H. (2017). Involvement of Organic Cation Transporters in the Kinetics of Trimethylamine N-oxide. *Journal of Pharmaceutical Sciences*, 106(9), 2542–2550. https://doi.org/10.1016/j.xphs.2017.04.067

Miyamoto, Y., Watanabe, H., Noguchi, T., Kotani, S., Nakajima, M., Kadowaki, D., Otagiri, M., & Maruyama, T. (2011). Organic anion transporters play an important role in the uptake of *p*-cresyl sulfate, a uremic toxin, in the kidney. *Nephrology Dialysis Transplantation*, 26(8), 2498–2502. https://doi.org/10.1093/ndt/gfq785

Morena, M., Creput, C., Bouzernidj, M., Rodriguez, A., Chalabi, L., Seigneuric, B., Lauret, C., Bargnoux, A. S., Dupuy, A. M., & Cristol, J. P. (2019). Randomised trial on clinical performances and biocompatibility of four high-flux hemodialyzers in two mode treatments: hemodialysis vs post dilution hemodiafiltration. *Scientific Reports*, 9(1), 1–13. https://doi.org/10.1038/s41598-019-54404-7

Ojeda, R., Arias-Guillén, M., Gómez, M., Vera, M., Fontseré, N., Rodas, L., Filella, X., Reverter, J. C., Lozano, F., Villamor, N., & Maduell, F. (2020). Study of Biocompatibility of Membranes in Online Hemodiafiltration. *Blood Purification*, 49(4), 400–408. https://doi.org/10.1159/000504954

Ok, E., Asci, G., Toz, H., Ok, E. S., Kircelli, F., Yilmaz, M., Hur, E., Demirci, M. S., Demirci, C., Duman, S., Basci, A., Adam, S. M., Isik, I. O., Zengin, M., Suleymanlar, G., Yilmaz, M. E., & Ozkahya, M. (2013). Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: Results from the Turkish OL-HDF Study. *Nephrology Dialysis Transplantation*, 28(1), 192–202. https://doi.org/10.1093/ndt/gfs407

Okuno, S., Ishimura, E., Kohno, K., Fujino-Katoh, Y., Maeno, Y., Yamakawa, T., Inaba, M., & Nishizawa, Y. (2009). Serum β2-microglobulin level is a significant predictor of mortality in maintenance haemodialysis patients. *Nephrology Dialysis Transplantation*, 24(2), 571–577. https://doi.org/10.1093/ndt/gfn521

Pecoits-Filho, R., Larkin, J., Poli-de-Figueiredo, C. E., Cuvello-Neto, A. L., Barra, A. B. L., Gonçalves, P. B., Sheth, S., Guedes, M., Han, M., Calice-Silva, V., de Castro, M. C. M., Kotanko, P., de Moraes, T. P., Raimann, J. G., & Canziani, M. E. F. (2020). Effect of hemodiafiltration on measured physical activity: primary results of the HDFIT randomized controlled trial. *Nephrology Dialysis Transplantation*, 36(6), 1057-1070.

Pecoits-Filho, R., Larkin, J. W., Figueiredo, C. E. P. de, Neto, A. L. C., Raimann, J. G., Barra, A. B., Canziani, M. E. F., Canhada, S., Campos, L. G. de, Woehl, J., Gonçalves, P. B., Han, H., & Moraes, T. P. de. (2019). Study Design and Baseline Characteristics of the Impact of HemoDiaFIltration on Physical Activity and Self-Reported Outcomes: A Randomized Controlled Trial (HDFIT Trial) in Brazil. *BMC Nefrology*, 20(1), 98-111.

Pelletier, C. C., Croyal, M., Ene, L., Aguesse, A., Billon-Crossouard, S., Krempf, M., Lemoine, S., Guebre-Egziabher, F., Juillard, L., & Soulage, C. O. (2019). Elevation of trimethylamine-N-oxide in chronic kidney disease: Contribution of decreased glomerular filtration rate. *Toxins*, 11(11), 635-649. https://doi.org/10.3390/toxins11110635

Penne, E. L., Visser, L., Van Den Dorpel, M. A., Van Der Weerd, N. C., Mazairac, A. H. A., Van Jaarsveld, B. C., Koopman, M. G., Vos, P., Feith, G. W., Kremer Hovinga, T. K., Van Hamersvelt, H. W., Wauters, I. M., Bots, M. L., Nubé, M. J., Ter Wee, P. M., Blankestijn, P. J., & Grooteman, M. P. C. (2009). Microbiological quality and quality control of purified water and ultrapure dialysis fluids for online hemodiafiltration in routine clinical practice. *Kidney International*, 76(6), 665–672. https://doi.org/10.1038/ki.2009.245

Penny, J. D., Grant, C., Salerno, F., Brumfield, A., Mianulli, M., Poole, L., & Mcintyre, C. W. (2018). Percutaneous perfusion monitoring for the detection of hemodialysis induced cardiovascular injury. *Hemodialysis International*, 22(3), 351–358. https://doi.org/10.1111/hdi.12632

Perl, J., Karaboyas, A., Morgenstern, H., Sen, A., Rayner, H. C., Vanholder, R. C., Combe, C., Hasegawa, T., Finkelstein, F. O., Lopes, A. A., Robinson, B. M., Pisoni, R. L., & Tentori, F. (2017). Association between changes in quality of life and mortality in hemodialysis patients: Results from the DOPPS. *Nephrology Dialysis Transplantation*, 32(3), 521–527. https://doi.org/10.1093/ndt/gfw233

Peters, S. A. E., Bots, M. L., Canaud, B., Davenport, A., Grooteman, M. P. C., Kircelli, F., Locatelli, F., Maduell, F., Morena, M., Nubé, M. J., Ok, E., Torres, F., Woodward, M., & Blankestijn, P. J. (2016). Haemodiafiltration and mortality in end-stage kidney disease patients: A pooled individual participant data analysis from four randomized controlled trials. *Nephrology Dialysis Transplantation*, 31(6), 978–984. https://doi.org/10.1093/ndt/gfv349

Petrie, J. J. B., Ng, T. G., & Hawley, C. M. (2008). Review Article: Is it time to embrace haemodiafiltration for centre-based haemodialysis? *Nephrology*, 13(4), 269–277. https://doi.org/10.1111/j.1440-1797.2008.00964.x

Pieroni, L., Levi Mortera, S., Greco, V., Sirolli, V., Ronci, M., Felaco, P., Fucci, G., De Fulviis, S., Massoud, R., Condò, S., Capria, A., Di Daniele, N., Bernardini, S., Urbani, A., & Bonomini, M. (2015). Biocompatibility assessment of haemodialysis membrane materials by proteomic investigations. *Molecular BioSystems*, 11(6), 1633–1643. https://doi.org/10.1039/c5mb00058k

Poesen, R., Claes, K., Evenepoel, P., De Loor, H., Augustijns, P., Kuypers, D., & Meijers, B. (2016). Microbiota-derived phenylacetylglutamine associates with overall mortality and cardiovascular disease in patients with CKD. *Journal of the American Society of Nephrology*, 27(11), 3479–3487. https://doi.org/10.1681/ASN.2015121302

Porrini, E., Ruggenenti, P., Luis-Lima, S., Carrara, F., Jiménez, A., de Vries, A. P. J., Torres, A., Gaspari, F., & Remuzzi, G. (2019). Estimated GFR: time for a critical appraisal. *Nature Reviews Nephrology*, 15(3), 177–190. https://doi.org/10.1038/s41581-018-0080-9

Ramponi, F., Ronco, C., Mason, G., Rettore, E., Marcelli, D., Martino, F., Neri, M., Martin-Malo, A., Canaud, B., & Locatelli, F. (2016). Cost-effectiveness analysis of online hemodiafiltration versus high-flux hemodialysis. *ClinicoEconomics and Outcomes Research*, 8, 531–540. https://doi.org/10.2147/CEOR.S109649

Reyes, H. B. (2020). Artículos de Revisión. *Revista Médica de Chile*, 148(1), 103-108. http://dx.doi.org/10.4067/s0034-98872020000100103.

Ronco, C., Brendolan, A., Milan, M., Rodeghiero, M. P., Zanella, M., & La Greca, G. (2000). Impact of biofeedback-induced cardiovascular stability on hemodialysis tolerance and efficiency. *Kidney International*, 58(2), 800–808. https://doi.org/10.1046/j.1523-1755.2000.00229.x

Ronco, Claudio, & Clark, W. R. (2018). Haemodialysis membranes. *Nature Reviews Nephrology*, 14(6), 394–410. https://doi.org/10.1038/s41581-018-0002-x

Ronco, C., Marchionna, N., Brendolan, A., Neri, M., Lorenzin, A., & Martínez Rueda, A. J. (2018). Expanded haemodialysis: From operational mechanism to clinical results. *Nephrology Dialysis Transplantation*, 33 (SUPPL. 3), iii41–iii47. https://doi.org/10.1093/ndt/gfy202

Roth, V. R., & Jarvis, W. R. (2000). Outbreaks of infection and/or pyrogenic reactions in dialysis patients. *Seminars in Dialysis*, 13(2), 92–96. https://doi.org/10.1046/j.1525-139x.2000.00027.x

Sakai, K. (2000). Dialysis membranes for blood purification. Frontiers of Medical and Biological Engineering. *The International Journal of the Japan Society of Medical Electronics and Biological Engineering*, 10(2), 117–129. https://doi.org/10.1163/15685570052061973

Saran, R., Robinson, B., Abbott, K. C., Agodoa, L. Y. C., Albertus, P., Ayanian, J., Balkrishnan, R., Bragg-Gresham, J., Cao, J., Chen, J. L. T., Cope, E., Dharmarajan, S., Dietrich, X., Eckard, A., Eggers, P. W., Gaber, C., Gillen, D., Gipson, D., Gu, H., Shahinian, V. (2017). US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. *American Journal of Kidney Diseases*, 69(3), A7–A8. https://doi.org/10.1053/j.ajkd.2016.12.004

Schiffl, H. (2019). Online hemodiafiltration and mortality risk in end-stage renal disease patients: A critical appraisal of current evidence. *Kidney Research and Clinical Practice*, 38(2), 159–168. https://doi.org/10.23876/j.krcp.18.0160

Shen, H., Liu, T., Morse, B. L., Zhao, Y., Zhang, Y., Qiu, X., Chen, C., Lewin, A. C., Wang, X. T., Liu, G., Christopher, L. J., Marathe, P., & Lai, Y. (2015). Characterization of Organic Anion Transporter 2 (SLC22A7): A Highly Efficient Transporter for Creatinine and Species-Dependent Renal Tubular Expression. *Drug metabolism and disposition: the biological fate of chemicals*, 43(7), 984–993. https://doi.org/10.1124/dmd.114.062364

Shi, Y., Tian, H., Wang, Y., Shen, Y., Zhu, Q., & Ding, F. (2019). Effect of ionic strength, pH and chemical displacers on the percentage protein binding of protein-bound uremic toxins. *Blood Purification*, 47(4), 351–360. https://doi.org/10.1159/000495343

Shroff, R., Bayazit, A., Stefanidis, C. J., Askiti, V., Azukaitis, K., Canpolat, N., Agbas, A., Anarat, A., Aoun, B., Bakkaloglu, S., Bhowruth, D., Borzych-Duzałka, D., Bulut, I. K., Büscher, R., Dempster, C., Duzova, A., Habbig, S., Hayes, W., Hegde, S., & Schmitt, C. P. (2018). Effect of haemodiafiltration vs conventional haemodialysis on growth and cardiovascular outcomes in children - The HDF, heart and height (3H) study. *BMC Nephrology*, 19(1), 199–209. https://doi.org/10.1186/s12882-018-0998-y

Smith, J., & Pfaendtner, J. (2020). Elucidating the Molecular Interactions between Uremic Toxins and the Sudlow II Binding Site of Human Serum Albumin. *Journal of Physical Chemistry B*, 124(19), 3922–3930. https://doi.org/10.1021/acs.jpcb.0c02015

Smith, J. R., Zimmer, N., Bell, E., Francq, B. G., McConnachie, A., & Mactier, R. (2017). A Randomized, Single-Blind, Crossover Trial of Recovery Time in High-Flux Hemodialysis and Hemodiafiltration. *American Journal of Kidney Diseases*, 69(6), 762–770. https://doi.org/10.1053/j.ajkd.2016.10.025

Stubbs, J. R., House, J. A., Ocque, A. J., Zhang, S., Johnson, C., Kimber, C., Schmidt, K., Gupta, A., Wetmore, J. B., Nolin, T. D., Spertus, J. A., & Yu, A. S. (2016). Serum Trimethylamine-N-Oxide is Elevated in CKD and Correlates with Coronary Atherosclerosis Burden. *Journal of the American Society of Nephrology*, 27(1), 305–313. https://doi.org/10.1681/ASN.2014111063

Suchy-Dicey, A. M., Laha, T., Hoofnagle, A., Newitt, R., Sirich, T. L., Meyer, T. W., Thummel, K. E., Yanez, N. D., Himmelfarb, J., Weiss, N. S., & Kestenbaum, B. R. (2016). Tubular secretion in CKD. *Journal of the American Society of Nephrology*, 27(7), 2148–2155. https://doi.org/10.1681/ASN.2014121193

Susantitaphong, P., Siribamrungwong, M., & Jaber, B. L. (2013). Convective therapies versus low-flux hemodialysis for chronic kidney failure: A meta-analysis of randomized controlled trials. *Nephrology Dialysis Transplantation*, 28(11), 2859–2874. https://doi.org/10.1093/ndt/gft396

Takura, T., Kawanishi, H., Minakuchi, J., Nagake, Y., & Takahashi, S. (2013). Cost-effectiveness analysis of on-line hemodiafiltration in Japan. Blood Purification, 35(SUPPL. 1), 85–89. https://doi.org/10.1159/000346358

Tanihara, Y., Masuda, S., Sato, T., Katsura, T., Ogawa, O., & Inui, K. ichi. (2007). Substrate specificity of MATE1 and MATE2-K, human multidrug and toxin extrusions/H+-organic cation antiporters. *Biochemical Pharmacology*, 74(2), 359–371. https://doi.org/10.1016/j.bcp.2007.04.010

Tao, X., Thijssen, S., Kotanko, P., Ho, C. H., Henrie, M., Stroup, E., & Handelman, G. (2016). Improved dialytic removal of protein-bound uraemic toxins with use of albumin binding competitors: An in vitro human whole blood study. *Scientific Reports*, 6(March), 2–10. https://doi.org/10.1038/srep23389

Tattersall, J. E., & Ward, R. A. (2013). Online haemodiafiltration: Definition, dose quantification and safety revisited. *Nephrology Dialysis Transplantation*, 28(3), 542–550. https://doi.org/10.1093/ndt/gfs530

Teft, W. A., Morse, B. L., Leake, B. F., Wilson, A., Mansell, S. E., Hegele, R. A., Ho, R. H., & Kim, R. B. (2017). Identification and Characterization of Trimethylamine-N-oxide Uptake and Efflux Transporters. *Molecular Pharmaceutics*, 14(1), 310–318. https://doi.org/10.1021/acs.molpharmaceut.6b00937

Thomas, G., & Jaber, B. L. (2009). Convective therapies for removal of middle molecular weight uremic toxins in end-stage renal disease: A review of the evidence. *Seminars in Dialysis*, 22(6), 610–614. https://doi.org/10.1111/j.1525-139X.2009.00665.x

Tomo, T. (2016). Biocompatibility of Hemodiafilters. *Contributions to Nephrology*, 189, 210–214. https://doi.org/10.1159/000450803

Urakami, Y., Kimura, N., Okuda, M., & Inui, K. I. (2004). Creatinine transport by basolateral organic cation transporter hOCT2 in the human kidney. *Pharmaceutical Research*, 21(6), 976–981. https://doi.org/10.1023/B:PHAM.0000029286.45788.ad

Vadakedath, S., & Kandi, V. (2017). Dialysis: A Review of the Mechanisms Underlying Complications in the Management of Chronic Renal Failure. *Cureus*, 9(8), 1-8. https://doi.org/10.7759/cureus.1603

Van Biesen, W., & Eloot, S. (2019). Enhanced removal of protein-bound uremic toxins using displacers: Road to success? *Clinical Journal of the American Society of Nephrology*, 14(3), 324–326. https://doi.org/10.2215/CJN.00500119

Van Gelder, M. K., Middel, I. R., Vernooij, R. W. M., Bots, M. L., Verhaar, M. C., Masereeuw, R., Grooteman, M. P., Nubé, M. J., van den Dorpel, M. A., Blankestijn, P. J., Rookmaaker, M. B., & Gerritsen, K. G. F. (2020). Protein-bound uremic toxins in hemodialysis patients relate to residual kidney function, are not influenced by convective transport, and do not relate to outcome. *Toxins*, 12(4), 234-254 . https://doi.org/10.3390/toxins12040234

Vanholder, R. C., & Glorieux, G. L. (2003). An Overview of Uremic Toxicity. *Hemodialysis International*, 7(2), 156–161. https://doi.org/10.1046/j.1492-7535.2003.00034.x

Vanholder, R., Laecke, S., & Glorieux, G. (2008). What is new in uremic toxicity? *Pediatric Nephrology*, 23(8), 1211–1221. https://doi.org/10.1007/s00467-008-0762-9

Vanholder, R., Massy, Z., Argiles, A., Spasovski, G., Verbeke, F., Lameire, N., Beige, J., Brunet, P., Cohen, G., De Deyn, P. P., Descamps-Latscha, B., Herget-Rosenthal, S., Hörl, W., Jankowski, J., Jörres, A., Rodriguez, M., Stegmayr, B., Stenvinkel, P., Wanner, C., & Zidek, W. (2005). Chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrology Dialysis Transplantation*, 20(6), 1048–1056. https://doi.org/10.1093/ndt/gfh813

Vaslaki, L., Karátson, A., Vörös, P., Major, L., Pethö, F., Ladányi, E., Weber, C., Mitteregger, R., & Falkenhagen, D. (2000). Can sterile and pyrogen-free on-line substitution fluid be routinely delivered? A multicentric study on the microbiological safety of on-line haemodiafiltration. *Nephrology Dialysis Transplantation*, 15(SUPPL. 1), 74–78. https://doi.org/10.1093/oxfordjournals.ndt.a027968

Villa, G., Rodríguez-Carmona, A., Fernández-Ortiz, L., Cuervo, J., Rebollo, P., Otero, A., & Arrieta, J. (2011). Cost analysis of the Spanish renal replacement therapy programme. *Nephrology Dialysis Transplantation*, 26(11), 3709–3714. https://doi.org/10.1093/ndt/gfr088

Wang, K., & Kestenbaum, B. (2018). Proximal tubular secretory clearance: a neglected partner of kidney function. *Clinical Journal of the American Society of Nephrology*, 13(8), 1291–1296. https://doi.org/10.2215/CJN.12001017

Ward, R. A., Vienken, J., Silverstein, D. M., Ash, S., & Canaud, B. (2018). Regulatory considerations for hemodiafiltration in the United States. *Clinical Journal of the American Society of Nephrology*, 13(9), 1444–1449. https://doi.org/10.2215/CJN.12641117

Weiner, D. E., Falzon, L., Skoufos, L., Bernardo, A., Beck, W., Xiao, M., & Tran, H. (2020). Efficacy and safety of expanded hemodialysis with the theranova 400 dialyzer: A randomized controlled trial. *Clinical Journal of the American Society of Nephrology*, 15(9), 1310–1319. https://doi.org/10.2215/CJN.01210120

Wikoff, W. R., Nagle, M. A., Kouznetsova, V. L., Tsigelny, I. F., & Nigam, S. K. (2011). Untargeted metabolomics identifies enterobiome metabolites and putative uremic toxins as substrates of organic anion transporter 1 (OAT1). *Journal of Proteome Research*, 10(6), 2842–2851. https://doi.org/10.1021/pr200093w

Wolley, M., Jardine, M., & Hutchison, C. A. (2018). Exploring the clinical relevance of providing increased removal of large middle molecules. *Clinical Journal of the American Society of Nephrology*, 13(5), 805–814. https://doi.org/10.2215/CJN.10110917

Wu, W., Bush, K. T., & Nigam, S. K. (2017). Key Role for the Organic Anion Transporters, OAT1 and OAT3, in the in vivo Handling of Uremic Toxins and Solutes. *Scientific Reports*, 7(1), 4939–4948. https://doi.org/10.1038/s41598-017-04949-2

Xue, H. Y., Duan, B., Li, Z.-J., & Du, P. (2020). High flux hemodialysis in elderly patients with chronic kidney failure. *World Journal of Clinical Cases*, 8(11), 2144–2149. https://doi.org/10.12998/wjcc.v8.i11.2144

Yamamoto, S., Kazama, J. J., Wakamatsu, T., Takahashi, Y., Kaneko, Y., Goto, S., & Narita, I. (2016). Removal of uremic toxins by renal replacement therapies: A review of current progress and future perspectives. *Renal Replacement Therapy*, 2(43), 1-8. https://doi.org/10.1186/s41100-016-0056-9

Zhao, S., Yan, L., Zhao, Z., Hou, M., & Rong, F. (2019). Laparoscopic hysterectomy in chronic renal failure patients with abnormal uterine bleeding. *Minimally Invasive Therapy and Allied Technologies*, 28(1), 41–45. https://doi.org/10.1080/13645706.2018.1467459