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Editorial

What is the role of expanded hemodialysis in renal replacement therapy in 2020?☆

¿Cuál es el papel de la hemodiálisis extendida en el tratamiento renal sustitutivo en 2020?

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Elimination of uremic toxins in dialysis

One of the primary functions of dialysis in the treatment of chronic kidney disease (CKD) stage 5 is the elimination of uremic toxins (UT). The kidney is the model to follow, capable of purifying continuously all types of UT without the elimination of albumin. The elements of this renal function are the glomerular filtration, the tubular functions and the elimination of urine. Dialysis is far from emulating these functions, although the capacity of blood purification has improved over the years.

Knowledge of UTs has advanced in the last decades[1,2].These molecules have been typified, the concentrations achieved in CKD have been measured, and their individual toxicity has been described[1–3]. UT retention is associated to cardiovascular risk[3–5], the main cause of mortality in dialysis patients. UTs are usually classified according to their molecular weight (MW) and whether they are bond to proteins, mainly albumin (Table 1)[1,2]. Recently, some authors propose to separate the middle size UT into two groups: molecules of medium and high molecular weight (MW)[6], setting the limit of these at 15,000 Da, according to different authors. This classification is of particular interest, since TUs of high MW have been associated with some of the main comorbidities derived from CKD and dialysis,[3]specifically inflammation and cardiovascular disease. Innovation of hemodialysis (HD) techniques and the introduction of new HD membranes allow the elimination of a greater number of medium-sized molecules as compared with the conventional HD.

During the early times of HD, the dialyzers-membranes available only allowed the removal of low-MW UTs. The *Low-flux* (LF) dialyzers purify significantly only the low-MW UT and have a coefficient of hydraulic permeability (Kf) of less than 20 mL/h/mmHg. Later on, there were incorporated the *high flux* (HF) dialyzers with a Kf greater than 20 mL/h/mmHg, capable of eliminating the so-called medium size molecules, with a MW up to 20,000 Da, including β_2-microglobulin (β_2-mG) and leptin. Thus, depending on the permeability of the dialyzer, two types of HD are distinguished, high (HD-HF) and low flow (HD-LF). Currently, we have numerous dialyzers with Kf greater than 50 mL/h/mmHg, called dialyzers of very high hydraulic permeability. The *Membrane Permeability Outcome* (MPO) study is the main exponent of the best clinical results of HF-HD compared to LF-HD[7,8]. Techniques with high convective transport and especially on-line hemodiafiltration (OL-HDF) with HF dialyzers, have been a step further, being able to purify some of the high-MW UT, and avoid the elimination of significant amounts of albumin. The *Online*

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Table 1 – Classification of uremic toxins and the clearance by the different techniques

	Small water soluble molecules	Middle molecules		Protein-bound molecules
		Middle molecules	Large molecules	
MW Daltons	<500 Urea Creatinine Match Oxalate Purines/ac. uric Guanidine (ADMA)	500–15,000 Atrial natriuretic peptide Endothelin PTH β_2 microglobulin Cystatin C	15,000–60,000 Leptin Myoglobin Light chains κ Interleukin 6 Hepcidin Light chains λ TNFα	P-cresol sulfate Indoleacetic Indoxylsulfate Pentosidine Neuropeptide
EPT / Clearance mechanism	LF -HD-, HF- HD /diffusion OL -HDF, HDx / diffusion and convection	HF-HD /diffusion diffusion HDF-OL, HDx / diffusion and convection	OL-HD, HDx / diffusion and convection	Adsorption, HFR / Diffusion, Convection and Adsorption

OL-HDF: online hemodiafiltration; HF- HD: high flow hemodialysis; LF -HD: low-flow hemodialysis; HDx: extended hemodialysis; HFR: hemofiltration with reinfusion of the ultrafiltrate; MW: molecular weight; EPT: extrarenal purification technique.

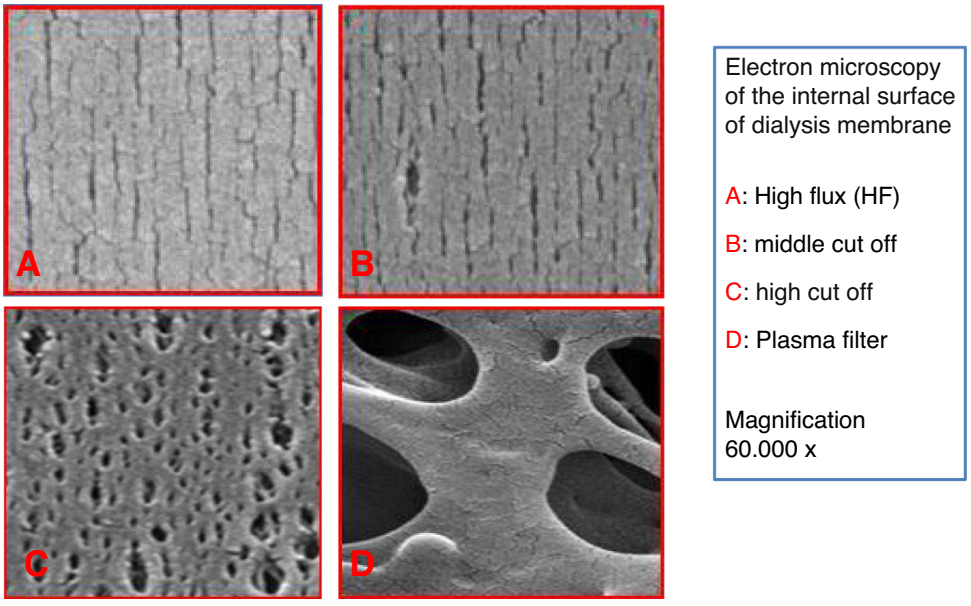


Fig. 1 – Electron microscopy of the inner surface of different types of membranes.

Hemodiafiltration Study (ESHOL) and other randomized trials have demonstrated the superiority, in terms of survival, of OL-HDF patients as compared with HF-HD and LF-HD[9,10]. We could conclude that elimination the UT of large MW and in a greater quantity is associated to a better prognosis of dialysis patients, independently of other morbidity and mortality cofactors.

During the last five years, a new type of membrane has been developed, with a higher *cut-off point* (CO), called mid-cut point (MCO), with the ability to remove high PM molecules, as well as it is done by high CO (HCO) membranes, used in myeloma, but capable of retaining albumin[11,12]. These new membranes have a high retention point or "*retention onset*". This concept is determined by the MW from which more than 10% of the solutes will be retained, that is, the MW for which the sieving coefficient (Sc) is 0.9. The size of the pores of the MCO membrane is intermediate between those of the HF and HCO membranes (Fig. 1). In addition, as we will explain below, these membranes have a dialyzer design that enhances internal convective transport[13]. Therefore, with these devices it is possible to obtain a clearance of medium and large molecules superior to that of HF dialyzers (Table 2). HD performed with MCO dialyzers has been called ëxtendedHD (HDx) because it is capable of increasing the range of MW of the UTs removed.

The objective of this review is to describe the characteristics of MCO membrane dialyzers, their performance in the elimination of UT, preliminary clinical results, and to position HDx among the HD techniques available today.

Technical development of dialyzers and dialysis

The innovation of dialyzers has been a key piece in the improvement of the HD procedure. A series of markers stood out for its effectiveness in eliminating UT. Classically, to assess

Table 2 – Elimination of uremic toxins measured by RR and clearances with HDx compared to HD-HF and HDF-OL

Reference n. º/1st author	Comparison	Characteristics	Design / methodology	Number of patients	Duration	Outcome
23 / Belmouaz M. et al.	OL- HDF Pol210H Ther500	Qb 300 mL / min	OL-HDF patients swithed to Ther	10	1 year in Ther	Similar RR of midle molecules Serum albumin and prealbumin unchanged
24 / Boschetti-de-Fierro A. et al.	HF -HD: Elisio17H™, FX CorDiax80 and 100™ Ther400 and 500	Qb 300 mL / min Qd 700 mL / min	Clearance : β2MG, myoglobin, LC κ and λ, IL-6	plasma in vitro		superior clearance of Ther for medium and large molecules
24 / Boschetti-de-Fierro A. et al.	HF -HD: Elisio21H and 25H™, FX CorDiax 120 and 1000™ Ther500	Qb 400 mL / min Qd 700 mL / min	Clearance : β2MG, myoglobin, LC κ and λ, IL-6	Plasma in vitro		Ther500 Superior clearance of molecules greater than myoglobin
24 / Boschetti-de-Fierro A. et al.	HDF (UF): Elisio17H™, FX CorDiax800™ Ther500 without Quf	Qb 300 mL / min Qd 700 mL / min Quf 100 mL / min	Clearance : β2MG, myoglobin, LC κ and λ, IL-6	Plasma in vitro		Similar clearance
24 / Boschetti-de-Fierro A. et al.	HDF (UF): Elisio21H and 25H™, FX CorDiax800™ Ther500 without Quf	Qb 300 mL / min Qd 700 mL / min Quf 100 mL / min	Clearance : β2MG, myoglobin, CL κ and λ, IL-6	In vitro plasma		Superior clearance for β2MG in HDF and in Ther500 for IL-6.
25,26 / Kirsh. et al.	HD FX CorDiax 80™ HD Ther400	Qb 300 mL / min Qd 500 mL / min	RR & Cl: MM: β2MG, Factor D, myoglobin, LC κ and λ, α_1-mG, YKL-40 and LMWM	39	Four sessions of HD- 4h each	RR & Cl superior with Ther in all the measured molecules, greater in those with the highest MW. Cl of P and urea higher in Ther
25, 26 / Kirsch et al.	HD Ther400 HD HF FX CorDiax 80™ HDF-OL FX CorDiax 800™	Qb 400 mL / min Qd 700/600 mL / min Quf total 21.4 L	RR & Cl: β2MG, Factor D, myoglobin, LC κ and λ, α_1-mG, YKL-40	39	Four sessions of 5 h	Cl and RR with Ther superior than HDF-OL and HD-HF
27 / Latosinska A. et al.	HF -HD-Revaclear400™ HD Ther400		DF: 30 L× 16 tests in CETs; LC-MS / MS; Dissolved molecules	8	DF collected during the 1st hour of the HD session	Higher concentration of proteins, albumin, B2MG, LPS, proapototic and proinflammatory molecules DF with Ther. DF with Ther produces worse viability and morphological changes in CETs
28 / Cordeiro ISF et al.	HF- HD polysulfoneHF Diacap™ 2 m^2 OL- HDF polysulfone HF Diacap™ 2 Ther400	Qb 350 mL / min Qd 800 mL / min Qinf 90-100 mL / min	Prospective-crossover RR, Cl and total extraction: urea, P, B2MG, albumin	16	4 + 4 + 4 weeks	greater CL of B2MG in OL- HDF and Ther; Similar total extraction with all three techniques.
29 / García-Prieto AM et al.	HF- HD- FX CorDiax 80™ OL- HDF FX CorDiax1000™ Ther500	Qb 450 mL / minOL -HDF: total Quf 28 L	RR: urea, Cr, P, β2MG, myoglobin, prolactin, cystatin, α1-glycoprotein Albumin in DF	18	1 session with each technique	No differences in urea, Cr or P. Ther and OL- HDF superior to HF- HD in all molecules, without differences between them. Albumin 0.03 g / session with Ther and 3.1 g in OL-HDF

– Table 2 (*Continued*)

Reference n. º/1st author	Comparison	Characteristics	Design / methodology	Number of patients	Duration	Outcome
30 / Maduell F. et al.	HF- HD FX CorDiax 80™ OL -HDF FX CorDiax 80™ HF -HD: PMMA HF- HD: Polyphenylene Ther400	Qb 434 mL / min Qd 400 mL / min OL -HDF Quf 31 L	RR: urea, Cr, β2MG, myoglobin, prolactin, α1-MG, α1-GP and albumin. Albumin in DF	21	One session with each technique	RR of urea and Cr greater with OL-HDF and Ther than with the other HF- HD; OL- HDF superior to HF -HD- and Ther. In general, Ther performance is between OL- HDF and HF-HD. Albumin loss between 0.54 g HF- HD FX CorDiax 80™ and 3.3 g with Polyphenylene
31 / Cho LF. et al.	HF -HD FX CorDiax 80™ Ther400	Qb 289–294 mL / min	RR: urea, β2MG, Vit.B12, CL κ and λ and free Hb	19 38	One session with each technique	Higher RR with Ther400 than with HF-HD in all measured molecules
32 / Kim TH et al.	HF- HD Rexeed-21A™ OL-HDF-pre Rexeed-21A™ Ther 400	250 mL / min	RR: urea, Cr, P, Uric Ac., β2MG, myoglobin, LC κ and λ, FGF-23, LC: CL λ	6	One session with each technique	Similar RR in all 3 techniques for small molecules; Higher RR in OL-HDF-pre for B2-mG and in Ther for myoglobin and LC λ.
33 / Lim JH et al.	HF- HD FX CorDiax 80-60™ Ther400	Qb 235 mL / min Qb 245 mL / min Qd 500 mL / min	Randomized prospective. RR: β2MG, LC κ and λ,	49	12 weeks	RR greater with Ther LC κ and λ, without differences in B2MG
34 / Willy K et al.	HF- HD Revaclear™ HCO1100 MCO400	In vitro plasma dialysis model	IL-6 in plasma and DF; Culture VSMC, MGP and OPN	Plasma enriched with LPS in vitro × 2		IL-6 decreases in plasma and increases in DF with MCO and HCO; induction of vascular calcification is reduced with plasma dialysed with MCO and HCO

α1-GP: α1-acid glycoprotein; TECs: tubular epithelial cells; Cl: clearance; LC: free κ or λ light chains; Cr: creatinine; Hb: hemoglobin; HCO: high cut-off dialyzer; HD: hemodialysis; HDF: hemodiafiltration; OL-HDF: post-dilution on line HDF; OL pre-HDF: on line predilution HDF; LC-MS / MS: liquid chromatography / mass spectrometry; DF: dialysis fluid; LPS: lipopolysaccharides; LMWM: low molecular weight molecules; MCO, mid-cut-point dialyzer; MGP: Gla protein; MM: medium and high MW molecules; OPN: osteopontin; P: phosphates; Pol 210H: Polyflux 210 H ™; Qb: blood flow; Qd: Dialysis liquid flow; Quf: Ultrafiltration flow; Ther: theranova™; RR: reduction percentage; VSMC: Vascular Smooth Muscle Cells.
The discrepancy regarding the elimination of uremic toxins is explained by the different methodology of the studies.

the elimination of low MW UT, the Kt / V or better the Kt corrected by body surface (Kt/BSA) is used[14]. The transition from HD-LF to HD-HF was marked by a Kf of the dialyzers greater than 20 mL / h / mmHg in the HF.

Convective transport is assessed by the total ultrafiltered volume (TUF) and the Sc coefficient for the different molecules,[15] being the Sc of β2-mG the most used. In this sense, the EUDIAL[16] group included among the requirements to define an effective OL-HDF, the use a dialyzer with a Sc for β2-mG greater than 0.6 and a TUF per session greater than 23 L. The importance of the amount of convective volume administered is due to the fact that it has been directly related to the clearance of middle molecules[17], and with the mortality of HD patients as already stated.

To typify dialyzers with MCO membranes, two markers have been used[11], the retention point or "*retention onset*" (MWRO) and the cut-off point (MWCO); the first is determined by the MW of the molecule whose Sc is of 0.9 or expressed in another way, the MW of the molecules that begin to be retained by a 10%, and the second, the MW that corresponds to a Sc of 0.1, close to the CO of the evaluated membrane (Fig. 2). These two markers have been used in the Sc curve for a membrane / dialyzer, because determining the MW at which a molecule begins to be retained and the MW of CO is very difficult. MCO dialyzers would have a Sc for β_2-mG close to 1 and 0.9 for myoglobulin.

The Sc of dialyzers depend on the conditions of the measurement. The type of plasma, blood flow (Qb), ultrafiltration flow (Quf) and the timing to obtain the sample are some of the factors that influence the result[15]. The comparison of dialyzers using their Sc is only reliable if the measurement conditions are similar. The technical data sheet of the devices, must specify the conditions of the Sc measurement.

The MCO membrane has been used in Theranova® (Ther) dialyzers, available in Spain for the last three years. The design favors internal filtration / retrofiltration, as a form of purification by convective transport[18], which has been called internal hemodiafiltration (iHDF)[19]. One of the ways to increase iHDF is to reduce the internal diameter of the hollow fibers, up to 180 μm diameter in these dialyzers, to increase internal resistances and achieve greater ration filtration/back-filtration. The internal radius of the hollow fibers is listed to the fourth power in the Hagen-Poiseuille equation that calculates the resistance of the blood to the passage through the capillaries. A long, narrow dialyzer with a hollow fiber diameter of 180 μm will cause a very large drop of pressure inside the hollow fiber, around 170 mmHg for 400 mL / min of Qb. Another way to increase internal filtration is to increase the hydraulic resistance in the dialysis fluid (DF) compartment, by increasing the density of the capillaries inside the dialyzer, between 55 and 60%[20], creating a pressure drop of 30 mmHg for a 500 mL / min of DF flow (Qd). The internal filtration is influenced directly by, Qb and Qd.

Although internal convective transport has been enhanced in the new MCO dialyzers, recent studies suggest that diffusive transport is the main mechanism for elimination of medium molecules in HDx[21]. It should be always remembered the interference of these two types of transport on the same membrane.

A requirement in the development of MCO membrane dialyzers was that they did not lose a significant amount of albumin. The high permeability must be compatible with only a minimal elimination of this protein, with a Sc less than 0.01. The loss of albumin is dependent on the size of the pores, its interaction with plasma and the transmembrane pressure (TMP). In OL-HDF, the prefilter pressure can reach 700 mmHg, being the main determinant of the loss of albumin. Dialyzers with MCO membranes should not be used at these pressures, so their use is not indicated in OL-HDF and isolated ultrafiltration. With techniques of HDF, MCO membranes can cause significant albumin losses. In any hemodialysis technique, the loss of albumin should be less than 4 g per session[6].

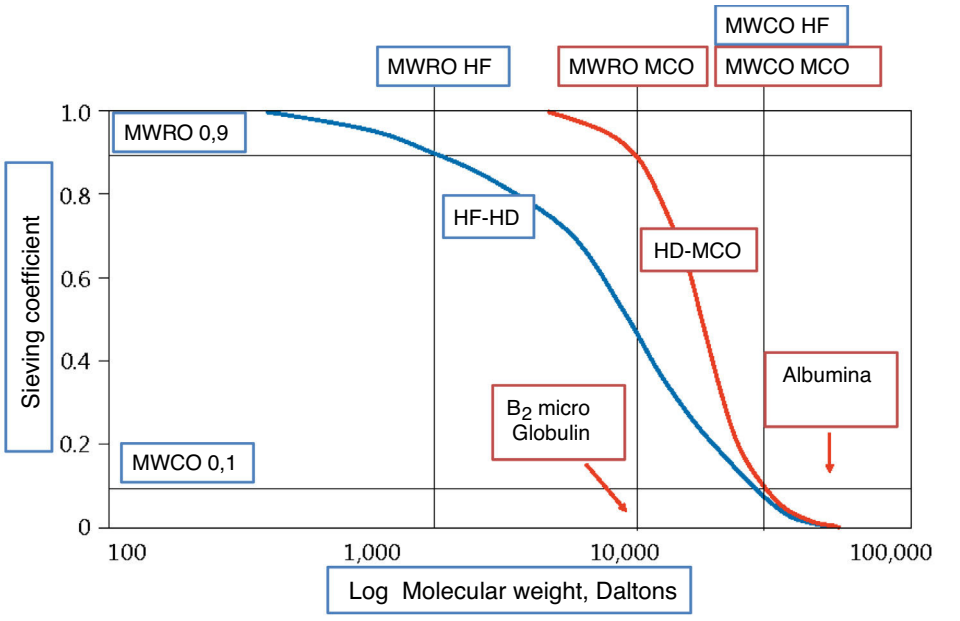
To assess the effectiveness of MCO dialyzers, we must continue to use Kt / V or Kt/BSA. In the clinic we cannot measure iHDF, although it has been estimated that for an MCO dialyzer, Ther400, with a Qb of 400 mL / min it would be 41.6 mL / min, and 53.1 mL / min with the Ther500[6,22], which would mean a four-hour HD session with an internal filtration of 9,984 mL and 12,744 mL, respectively, and the programmed ultrafiltration would have to be added. Taking into account that the Sc of this dialyser for β2-mG is > 0.9, the calculated clearance of β2-mG would be similar to that of OL-HDF. The Qb, therefore, would also be an important determinant of the purifying efficiency with these dialyzers. The preHD concentration of β2-mG could be useful, and should be kept between 20 and 30 mg / L, except in situations of hyperproduction of β2-mG. With MCO dialyzers, Kf has no longer the importance of HF dialyzers; the relationship of Kf and Sc is not satisfactory.

The use of HF-HD and OL-HDF has required other advances in dialysis. Among them, the machines need a precise control of ultrafiltration (UF), a DF with bicarbonate and ultrapure quality. HDx also requires a dialysis monitor with these improvements, although, unlike OL-HDF, it does not require a DF infusion system tied to UF monitoring. The HDx can be performed with any modern HD machine with endotoxin filters.

Clearance of Uremic toxin and the clinical evidences of HDx

The two dialyzers available in Spain with an MCO membrane, composed of polyarylethersulfone and polyvinylpyrrolidone, free of bisphenol A (BPA), are the Ther400 and the Ther500. Both have an internal diameter of the hollow fiber of 180 μm and 35 μm of wall thickness. The Ther400 has a surface area of 1.7 $m^2$and a Kf of 48 mL / h / mmHg, and the Ther500 has a surface area of 2.0 $m^2$and a Kf of 59 mL / h / mmHg (*in vitro* with bovine blood, Ht. 32 % Pt 6 g/ dL and 37 °C). The Sc is 1 for β_2-mG, 0.9 for myoglobin and 0.008 for albumin (measured with human plasma, a Qb 300 mL / min and UF 60 mL / min).

The clearance of UT with these dialyzers has been compared with that of the HF-dialyzers and with OL-HDF (Table 2)[23–34]. HD-HF has similar or slightly inferior results regarding the elimination of molecules of low MW in contrast to OL-HDF and HDx, measured by the proportional o reduction in the concentration of the molecules before and after HD (RR) or by measuring their clearance. Regarding the middle molecules, post-dilution OL-HDF and HDx are superior to HF-HD. If OL-HDF is performed with high convective trans-



MWRO: molecular weight rejected by a 10 %, MWCO molecular weight rejected by a 10 %,

Fig. 2 – Comparison of the Sieving coefficients of the membranes of high efficiency (*high-flux*) and those of the medium cut-off point (MCO).

port, OL-HDF is superior to HDx. Regarding large molecules, as the MW increases, HDx surpasses OL-HDF, as for example with λ–light chains.

The characteristics of dialysis that make OL-HDF superior to HDx have been evaluated[34]. With a Qb of 350 mL / min, OL-HDF is superior to HDx in terms of the percentage reduction (RR) of the molecules, evaluated by means of a « *Global Removal Score* » (GRS), from 80.6 mL / min of Quf, with a Qb of 400 mL / min it would be from 74.1 mL / min. The main problem with this comparison is in the composition of the GRS, which includes, among other molecules, urea. If the RR of large molecules, such as λ light chains and interleukin-6 (IL-6), is analyzed, HDx would be superior to OL-HDF[24–26]. The influence of the different large UTs on morbidity and mortality remains to be evaluated.

With MCO dialyzers, albumin loss in the DF is usually greater than in HF-HD and OL-HDF, in any case it is less than 3.5 g / session, between 0.03 and 3.15 g / session[25,29,30,32,35,36]. Albumin losses is dependent on the type of membrane and transmembrane pressures, and with OL -HDF it can exceed 10 g / 4 h with some dialyzers[37]. In HDx patients, after an initial drop, the serum albumin is maintained[24,38]. At 12 weeks and 12 months with MCO membranes, no significant changes in albuminemia have been detected[31,33]. In the work of Bunch et al.[39]performed in 638 patients, after one year, it was fond a decrease of 3.5%.

One question that arises with MCO membranes is whether, while they cleanse more UT of medium and high MW than HD-HF, they remove more clotting factors, nutrients, drugs, and other molecules that are beneficial to the body. An *in vitro* study suggests that the change from HF- HD to Ther500 does not require adjustment in anticoagulation or other drug such as vancomycin[40]. The changes in insulin and erythropoietin concentrations would be similar with Ther500, HD-HF with Polyflux210H™ and HDF with Fx CorDiax 800™[40].

Although the ability of MCO dialyzers to retain endotoxins and other pyrogenic substances has been reported[41,42], given the significant back-filtration of these dialyzers, it is reasonable to use ultra-pure DL.

Clinical results with HDx

There are not many studies on the clinical impact of HDx at medium and long term (Table 3)[23,28,31,33,38,43–45]. The study that includes most number of patients is the Colombian COREXH Registry,[39] they recruit 992 patients dialyzed with HDx and 638 complete one year of follow-up (Table 3). The mortality is 8.54 per 100 patient-year, this is low as compared to other similar studies using other HD techniques[46,47]. The admission rate was 0.79 / patient-year and 6.91 days / patient-year[39]. There were no adverse effects described with HDx[25,39,43], nor hypersensitivity reactions to synthetic membranes / polysulfones[48]. Nevertheless, since it is a synthetic membrane, hypersensitivity reactions may occur.

The perceived quality of life has been assessed in a prospective study[33] in which 49 patients were randomized, 24 were dialyzed with Ther400 and 25 with HF-HD with the FX CorDiax 80-60™. The test, Kidney Disease Quality of Life Short Form-36 (KQDOL-36) with 36 items was performed at baseline and at 12 weeks. Ther400 patients expressed a better quality of life, mainly on the physical domains, with less itching and sleep disturbances.

Cho et al.[31]did not find significant differences in the preHD concentration of UTs in patients on Ther400 and those using

Table 3 – Clinical aspects of HDx

Reference n.°/1st author	Comparisons	Characteristics	Design	Number of patients	Duration	Outcome
23 / Belmouaz M. et al.	OL- HDF Pol210H Ther500	Qb 300 mL/min	OL-HDF patients switched to Ther	10	1 year in Ther	RR similar for midlle molecules Albumin and prealb unchanged
43 / Cozzolino et al.	HF- HD: (Fx80, Fx100) Ther400		Prospective and crossover	20	3 + 3 months	Less number of infections, and reduction of IL-1β and IL-6 in Ther 400, with greater decrease of albumin
38 / Zickler D. et al.	HF-HD: Revaclear400 ≈Ther400		Prospective and crossover	Completed in 48 (23 + 24)	4 + 8 weeks	Ther400 modulates the inflammation better than HF-HD: TNFα and IL6mRNA-RQ in PBMCs. < Pro-inflammatory CK
44 / Belmouaz M. et al.	HF-HD: Elisio 21H™ Ther	Qb 317 mL / min Qd 500 mL / min	Prospective, randomized, crossover	40	3 + 3 months	Lower preHD concentrations of β2-mG, oxidized LDL, κ and λ LC and albumin with Ther
28 / Cordeiro ISF et al.	HF-HD OL- HDF Ther		RR, Cl and total extraction: urea, P, B2mG, albumin	16	4 + 4 + 4 weeks	PreHD serum levels of urea, P, β2-mG and albumin similar with the three techniques.
31 / Cho LF. et al.	HF-HD FX CorDiax 80™ Ther400	Qb 289–294 mL / min	PreHD concentration: urea, β2MG, Vit.B12, LC κ and λ, albumin and free Hb	19 38	12 months	Na, K and ferritin decreased significantly in the Ther group. No changes in the rest of the molecules. No control of RRF
53 / Florens N. et al.	Ther		Observational experience	5,191 sessions	4 months	Automatic + manual priming No adverse effects. Specific clinical improvement.
33 / Lim JH. et al.	HF-HD FX CorDiax 80-60™ Ther400	Qb 235 mL / min Qb 245 mL / min Qd 500 mL / min	Randomized prospective: QoL short form 36. Pruritus questionnaire	49	12 weeks	Better QoL with Ther, mainly about physical components. Improved itching and less sleep disturbances with Ther
39 / Bunch A. et al.	Ther	Qb 350 mL / min Qd 500 mL / min	Prospective morbidity and mortality. Evolution of clinical and biochemical parameters	992 included, 638 completed the follow-up	1 year	Mortality: 8.54 per 100 per year Admissions: 0.79 events per year; 6.91 days per year. Serum albumin decreases 3.5%. No AE

β2-microglobulin: β2-mG; LC: free light chains; CK: cytokines; AE: adverse effects; RRF: residual renal function; Hb: hemoglobin; HDx: extended hemodialysis; IL6mRNA-RQ: IL-1β; IL-6: interleukin 6;Oxidized LDL: oxidized low-density lipoprotein; P: patients.. phosphate???; PBMCs: peripheral blood mononuclear cells; Pol 210H: Polyflux 210 H™; Qb: blood flow; Qd: dialysis fluid flow; QoL: quality of life short questionnaire 36 items; Quf: ultrafiltration flow; RR: percent reduction; Ther: Theranova; TNF-α: Tumor-necrosis factor alpha; β2-mG: β-2-microglobulin; IL-6: interleukin-6; mRNA: messenger RNA.

FX CorDiax 80 after 12 months. The low serum concentrations of β_2-mG, 25.6 mg / L, which rise to 28.4 mg / L per year are noteworthy; these concentrations are common in OL-HDF or when there is significant residual renal function (RRF); this information was not provided, and could mask the effect of the Ther400 since it decreases over time.

Pro-inflammatory parameters has been reported to improve with HDx[38]. One of the factors that explain the loss of RRF in dialysis is inflammation[49]. Some UT with high MW cause injury to renal tubules and therefore will decrease RRF[2,3,27]; their greater clearance by the MCO dialyzers[27] could preserve RRF, a matter that will have to be investigated.

The induction of vascular calcification is reduced with plasma dialyzed with MCO and HCO[34], so a possible beneficial effect of HDx to avoid vascular calcifications should be evaluated.

At the closing of this manuscript, there are 16 ongoing HDx studies, registered in the *ClinicalTrials*[50]. Six of these are completed and eight are recruiting patients. In six trials HDx was compared with HF-HD, in four with HDF and in one with both techniques. Some focus on specific aspects such as: anticoagulation, preservation of RRF, calcifications and mineral metabolism or symptoms. Among them is the Spanish multicenter, open, prospective, randomized study MoTHER to explore morbidity and mortality in dialysis patients with HDx compared with OL-HDF.

Key features of the HDx

What makes HDx different from other forms of HD Its ability to remove large molecules, high MW UT (Table 1). The HDx can be defined as a high Sc HD, tuning further, with a MWRO in the range of high MW UTs. Therefore, the Sc of myoglobin, ≥ 0.9, should be used to differentiate it from conventional HF-HD. The HDx is therefore a high-Sieving HD. Myoglobin is a 17,000 Dalton molecule that is easy to measure and belongs to the low range of high MW molecules.

What is the position HDx as a dialysis technique

There is little clinical evidence to determine what types of patients may benefit the most from HDx. Based on previous experience with other high-level clearance of UT techniques, such as OL-HDF, we could propose some aspects to evaluate in future studies. 1. Patients without a significant RRF; 2. Patients with the prospect of staying on hemodialysis for years, for example, not candidates for kidney transplantation; 3. Patients with a sufficient nutrients intake ; 4. Patients with much comorbidity; 5. As an alternative to OL-HDF in cases where high convective transport cannot be guaranteed (elevated Hb, suboptimal Qb)[51]. The cases with greater comorbidity that could benefit from HDx would be those that have a clear relationship with the retention of high-MW UT: chronic inflammation; resistance to EEA; restless leg syndrome, secondary immunodeficiency, and cardiovascular disease[52].

The HDx competes with OL-HDF. The use HDx would be indicated in patients in whom it is not possible to achieve an adequate convective volume per session (23 L) or when OL-HDF is suspended for safety reasons.

Good results have been reported in people with certain pathologies[43,53]: pruritus[33], post-HD asthenia, anorexia, restless legs syndrome, light chain myeloma[54], rhabdomyolysis, severe inflammation. Some of these indications coincide with our own experience.

The superiority of HDx over HF- HD- in eliminating high MW UT, its easy implementation and its safety suggest creating a new section in the classification of HD techniques. The HDx is not a “conventional” HD in the sense that is not within established standards of HD. With the existing data, the HDx should be in a new category of HD. Clinical studies on morbidity and mortality are needed to demonstrate the non-inferiority of HDx as compared with OL-HDF[50].

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