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Effect of High Dose Hemodiafiltration on Adiponectin and Complement Factor D Removal

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ABSTRACT

Background: Adiponectin and complement factor D are harmful large middle molecules that accumulate in patients with end stage renal disease. High-dose hemodiafiltration (HDF) has recently shown a clear survival benefit.

Objective: In this study we aimed to compare the removal of adiponectin and complement factor D in patients on HDF versus high flux hemodialysis (HD) using two different high flux dialysers.

Patients and Method: This is a cross over clinical trial. Twenty hemodialysis patients were enrolled. Dialyser and treatment efficacies were examined during a mid-week session with the following treatments HD FX 80, HD H4, HDF FX80, HDF H4. Treatment efficacy was assessed by calculating the reduction ratio (RR) of adiponectin and complement factor D before and after each session.

Results: Twenty dialysis patients aged 50.5 ± 10.4 years. During HDF urea reduction ratio (URR) was 70.4 ± 6.8 compared to 65.1 ± 7 during HD. Adiponectin RR using HDF FX80 was 48.1 ± 9.3 compared to 32.2± 9 with HD FX80, p <0. 001. Adiponectin RR using HDF H4 was 46.7 ±12.2 compared to 31.1± 9.4 with HD H4, p<0. 001. Complement factor D RR using HDF FX80 was 48.1 ± 13 compared to 29.8±9.6 with HD FX80, p<0.001. Complement factor D RR using HDF H4 was 46.7±12.2 compared to 26.6 ± 7.5 using HD H4, p<0.001.

Conclusion: High- dose HDF offered better removal of adiponectin and complement factor D compared to high flux HD. No difference was observed between the two high flux dialysers used.

Keywords: Adiponectin, Complement factor D, High flux dialysis, High-dose hemodiafiltration.

INTRODUCTION

The removal of uremic toxins, including small, medium, and large sized molecules, is the main objective of dialysis. Dialysis patient mortality is still rather high. At one, three, and five years, the survival probability is around 90, 70, and 50%, respectively [(1)]. This can be partially explained by the number of people on dialysis and the rising incidence of comorbid conditions like diabetes and hypertension, which raise the risk of cardiovascular disease. The chronic inflammatory state exacerbated by the accumulation of toxins, middle, and large sized molecules also leads to increased morbidity and mortality [(2)].

Uremic solutes are divided into three major classes according to size: small water-soluble compounds (<0.5 kDa), middle molecular substances (0.5-40 kDa) and protein bound solutes. Most of HD techniques remove small water-soluble molecules and urea clearance as a measurement for dialysis dose [(3)].

HDF offers the elimination of bigger molecules gained by hemofiltration in addition to the high diffusive clearance of tiny molecules obtained in HD [(4)]. High-flux (HF) membranes used with HDF have high water and solute permeability for middle-sized molecules [(5)]. Since bigger molecules are more dependent on convective transport and have slower diffusional removal than small molecules, HDF enhanced medium molecule clearance [(6)].

It is well recognized that a number of toxins, namely big intermediate molecules ranging in size from 15 to 60 kDa, are retained in end-stage renal failure. These molecules are not well removed by traditional dialysis and have been linked to cardiovascular disease and inflammation. Numerous cytokines, adipokines, growth factors, and other signaling proteins are among these substances. In comparison to people with normal renal function, the levels of these proteins might be significantly raised in uremia. Specifically, most cytokines and inflammatory proteins are 2–10 times greater in uremia [(7)]. There is inconsistent data about HDF's benefit to survival. A recent study found that using high dosage HDF with large quantities of replacement fluid, as opposed to high flux HD, decreased mortality from all causes [(8)].

Adiponectin is a 30-kDa adipose-derived hormone with anti-inflammatory and antiatherogenic effects. Higher levels have been associated to decreased incidences of myocardial infarction in males with and without diabetes [(9)]. Adiponectin enhances insulin sensitivity and has a favourable effect on lipid profile and body weight. This association was not consistent in haemodialysis patients where adiponectin was linked to mortality [(10)].

Complement D is the rate-limiting step in the synthesis of C3 convertase and is a component of the alternative complement pathway. In individuals with ESRD, it is markedly high, which causes severe complement dysregulation. It is well recognized that myocardial ischemia-reperfusion damage and endothelial dysfunction are related to complement activation and deposition [(11)].

This study aims to compare the removal of large middle molecules adiponectin and complement factor D in patients on HDF versus high flux hemodialysis using two different high flux dialysers.

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PATIENTS AND METHODS

This is a prospective, cross over, open label clinical trial conducted in Ain Shams University Hospital Dialysis Unit from March 2023 till November 2023.

Twenty patients older than 18 years of age who have been on regular haemodialysis were enrolled. These patients were on high flux filter FX 60 for more than 6 months on a regular schedule of 4-hour sessions thrice weekly. All patients had arteriovenous fistula (AVF). These patients had no residual kidney function.

Patients with active infection, malignancy, dialysis vascular catheters, decompensated heart failure, liver failure and patients who were non-complaint on haemodialysis were excluded.

High flux FX80 dialyser was compared with High flux H4 dialyser in both Hemodialysis and online post-dilution Hemodiafiltration modalities. Primary outcome was the removal of Adiponectin and Complement factor D. Blood samples for Adiponectin, complement factor D, potassium, bicarbonate, and urea were withdrawn before and after each session.

Blood samples were taken from the arterial line in the beginning and 30 seconds after decreasing Qb between 50 and 80 mL/min during a midweek dialysis session. There was a two-week washout period between sessions. Patients had the following sessions in a random order. HD session with Platinum H4 (HD H4) and FX80 (HD FX80) and an HDF session with Platinum H4 (HDF H4) and FX80 (HDF FX80).

Complete blood count, Albumin, Calcium, phosphate, and Parathyroid hormone levels (PTH) were measured. All patients had full history and examination recorded including cause of end stage Renal disease (ESRD), HD and HDF related parameters (Ultrafiltration volume, blood flow rate, body weight, convection volume and substitution volume) were documented.

The dialysis sessions were 4-hour sessions using bicarbonate dialysate and anticoagulation with low molecular weight heparin. We use 5008S CorDiax machines. HDF sessions parameters were as follows substitution goal >23 litres, blood flow > 300 ml/min and dialysate flow rate >500ml/min.

Dialyser characteristics:

We compared the two dialysers we frequently use in our unit. Platinum H4 dialyser made of enhanced micro undulated polysulfone hollow fibres with steam sterilization and 1.8m2 surface area and compared it to FX80 dialyser made of helixone membrane with housing material polypropylene with steam sterilization and 1.8 m2 surface area (Table 1).

Table (1): Dialyser characteristics

Dialyser	Fresenius FX 80	Platinum H4
Membrane material	Helixone	Microundulated polysulfone
Surface area (m^2)	1.8	1.8
Membrane wall thickness(um)	35	40
Membrane inner diameter(um)	185	200
Flux	HF	HF
B2m (11.8kD)	0.8	0.85
Albumin (66.5KD)	0.001	<0.001
UF coefficient (mL/h/mmHg)	53	58
KoA urea(mL/min2)	1429	1394
Sterilization	Steam	Steam

B2m beta 2 microglobulin, UF: Ultrafiltration, KoA mass transfer area coefficient

Calculations:

The post-dialysis concentrations of complement factor D and adiponectin were corrected for hemoconcentration according to **Bergström and Wehle** [12].

$$\text{A Post. C} = \frac{\text{A post}}{\frac{1+\triangle BW}{0.2 \times BW\ post}}$$

A post c: Adiponectin level post session after correction for net UF, A post is adiponectin post session, BW is the body weight, BW post is the body weight after ultrafiltration.

$$\text{Factor D Post. C} = \frac{\text{Factor D post}}{\frac{1+\triangle BW}{0.2 \times BW\ post}}$$

Factor D post c: Complement factor D post session after correction for net UF, Factor D post is factor D post session, BW is body weight, BW post is the body weight after ultrafiltration.

The following equation is used to calculate reduction ratio.

RR= A pre- A post/A Pre X100

RR: Reduction ratio, A post is Adiponectin post treatment, A pre is Adiponectin pre-treatment. Reduction percentages were computed by multiplying the reduction ratio by 100%.

RR= Factor D pre- Factor D post /Factor D Pre X100

RR: Reduction ratio, Factor D post is Factor D post treatment, Factor D pre is Factor D pretreatment. The reduction ratio was multiplied by 100% to determine the reduction percentages.

Laboratory measurements:

All blood samples were taken and transported to testing facilities under standardized circumstances.

The level of Adiponectin was measured using DEVELOP Human Adiponectin (ADP) ELISA kit Catalog No: DL-ADP-Hu. The kit is a sandwich enzyme immunoassay designed for quantitative detection of ADP in human blood, plasma, tissue homogenates, cell lysate, cell culture supernates, and other biological fluids.

The level of Complement factor D was measured using DEVELOP Human Complement Factor D(CFD)ELISA Kit Catalog No: DL-CFD-Hu. The kit is a sandwich enzyme immunoassay for the quantitative detection of ADP in human blood, plasma, tissue homogenates, cell lysate, cell culture supernatants, or other biological fluids.

Ethical approval:

Ain Shams Ethics Committee authorized the study (number of approval FMASU MD270/2022). For every participant, written informed permission was acquired. The Helsinki Declaration was followed when conducting the study.

Statistical analysis

IBM SPSS version 20.0 was used to input and evaluate the data. Numbers and percentages were used to represent categorical data. The Shapiro-Wilk test was used to determine if the continuous data were normal. Three ways were used to express quantitative data: mean±SD, median, and range (lowest and maximum). When comparing two periods of data that are regularly distributed quantitatively, use the Paired T-test. The 5% level was used to assess the results' significance.

RESULTS

Baseline characteristics

In this crossover trial twenty haemodialysis patients participated 18 were males. The mean age was 50.5 ± 10.4 years. The mean dialysis vintage was 3.8 ± 1.2 yrs. The Aetiology of ESRD was hypertension in 55 % of the cases.

Mean dry weight was 84.8 ± 17.3 kg. Mean ultrafiltration volume was 2.7 ± 0.83 L. During HDF treatment, mean convection volume was 24.3 ± 1.1 L and post dilution substitution volume was an average of 21.6 ± 0.8 L, Blood flow rate average was 352 ± 8 ml/min as shown in table 2.

Table (2): Characteristics of patients

	No. (%)
Gender	
Male	18 (90%)
Age *(yrs)*	50.5 ± 10.4
Etiology	
Diabetes	4 (20%)
Hypertension	11 (55%)
Unknown	2 (10 %)
Vesicoureteric reflux	1 (5%)
Glomerulonephritis	1 (5%)
ADPKD	1 (5%)
Obstructive uropathy	1 (5%)
Analgesic nephropathy	1 (5%)
Dialysis vintage *yrs*	
Dialysis parameters	3.8±2
Ultrafiltration volume (UF) *L*	2.7 ± 0.83
Dry weight *Kg*	84.8 ± 17.3
Convection volume *L*	24.3 ± 1.1
Substitution volume *L*	21.6 ± 0.84
Blood flow *ml/min*	352 ± 8
Dialysate flow *ml/min*	520 ± 18
Laboratory data	
Hemoglobin (Hb) *g/dl*	10.9 ±1.2
White cell count (WCC)	6.9 ±1.7
Platelet count (Plt)	217± 30
Albumin (Alb) *g/dl*	3.8 ± 0.37
Calcium (Ca) *mg/dl*	8.8±0.48
Phosphate (Ph) *mg/dl*	4.28 ± 1
Parathyroid hormone (PTH) *pg/ml*	505.5 (149 – 1912)
Sodium (Na) *mmol/L*	136.4 ± 3.5

Data were expressed in Mean ± SD. or Median (Min. – Max.)
ADPKD: Autosomal dominant polycystic kidney disease

Predialysis parameters and change in solutes before and after HD and HDF

Mean Haemoglobin level was 10.9 ± 1.2 gm/dl, Albumin was 3.8 ± 0.37 mg/dl, Phosphorus was 4.28 ± 1 mg/dl, Calcium 8.8 ± 0.48 mg/dl, median PTH was 505 pg/ml (149-1912) as shown in table 2.

Urea reduction ratio (URR) in HDF was 70.4 ± 6.8 compared to HD only 65.1 ± 7 as shown in table 3.

Potassium decrease was more with HDF, but no significant difference was found between the two high flux dialysers. Percentage potassium decrease with HDF FX80 was 28.3 ± 6 and 24.3 ±5.1 with HD FX80, p 0.003. Potassium decrease with HDF H4 was 29 ± 5.7 compared to 23.3 ± 4.8 with HD H4, p 0.005 as shown in table 4. Bicarbonate increase with HDF FX80 was 39.4 ± 14.6 and 32.7 ± 7.3 with HD FX80, p 0.028. Bicarbonate increase with HDF H4 was 32.9 ± 6.8 compared with 32.1 ± 7.7 with HD H4 as shown in table 3.

Table (3): Potassium and bicarbonate change during HDF and HD

		HDF	HD	t	p
FX80	**Potassium k mmol/L**				
	Pre	5.6 ± 0.51	5.3 ± 0.38	3.260*	
	Post	4 ± 0.50	4 ± 0.38	0.251	
	Percentage decrease	28.3 ± 6	24.3 ± 5.1	3.389*	0.003*
	Fold change	1.2 ± 0.39			
	Bicarbonate HCO3 (mEq/L)				
	Pre	17.8 ± 1.4	18.1 ± 1.2	0.905	
	Post	24.6 ± 1.2	23.9 ± 1.2	2.024	
	Percentage Increase	39.4 ± 14.6	32.67 ± 7.3	2.382*	0.028*
	Fold change	1.2 ± 0.38			
Platinum H4	**Potassium k mmol/L**				
	Pre	5.4 ± 0.37	5.4 ± 0.50	0.426	
	Post	3.8 ± 0.40	4.2 ± 0.42	2.604*	
	Percentage decrease	29 ± 5.7	23.3 ± 4.8	3.202*	0.005*
	Fold change	1.3 ± 0.46			
	Bicarbonate HCO3 (mEq/L)				
	Pre	18.8 ± 0.86	18.1 ± 1		
	Post	25 ± 0.91	23.9 ± 1		
	Percentage Increase	32.9 ± 6.8	32.1 ± 7.7	0.408	0.688
	Fold change	1.1 ± 0.30			

Data were expressed in Mean ± SD. t: Paired t-test
p: p value for comparing between HDF and HD
*: Statistically significant at $p \leq 0.05$

Changes in Adiponectin and Complement factor D before and after HD and HDF

We compared Adiponectin and Complement Factor D Reduction ratio between high flux HD and HDF. There was more reduction of Adiponectin and complement factor D after HDF compared to high flux HD as shown in Figure (1) and (2).

Adiponectin RR using HDF FX80 48.1 ± 9.3 ng/ml compared to 32.2± 9 ng/ml using HD FX80, p <0. 001.Adiponectin reduction ratio using HDF H4 is 46.7 ±12.2 compared to 31.1± 9.4 with HD H4, p<0.001.

Complement factor D RR using HDF FX80 is 48.1 ± 13ng/ml compared to 29.8±9.6 ng/ml, p<0.001. Complement Factor D reduction ratio using HDF H4 is 46.7±12.2 compared to using HD H4 26.6 ± 7.5 ng/ml, p<0.001 as shown in table 3.

There was however no difference when comparing the two high flux dialysers. Adiponectin reduction ratio using HD FX80 was 32.2± 9 compared to HD H431.1 ±9.4, p 0.7. Complement D reduction ratio was HD FX80 29.8 ± 9.6 compared to 26.6±7.5 HD H4, p 0.2.

Adiponectin reduction ration HDF FX80 48.1± 9.3compared to 46.7± 11.5 HDF H4, p 0.14. Complement D reduction ratio HDF FX80 48.2 ± 12.9 compared to 46.7 ± 12.2 HDF H4, p 0.5.

Table (4): Complement Factor D and Adiponectin reduction ratio.

	HDF	HD	t	p
Complement D RR				
FX80	48.2 ± 12.9	29.8 ± 9.6	5.669*	<0.001*
H4	46.7 ± 12.2	26.6 ± 7.5	6.981*	<0.001*
p0	0.547	0.192		
Adiponectin RR				
FX80	46.7 ± 11.5	31.1 ± 9.4	5.325*	<0.001*
H4	48.1 ± 9.3	32.2 ± 9	5.624*	<0.001*
p0	0.143	0.705		

Data were expressed in Mean ± SD. t: Paired t-test
p: p value for comparing between HDF and HD
p_0: p value for comparing between FX80 and H4
*: Statistically significant at $p \leq 0.05$

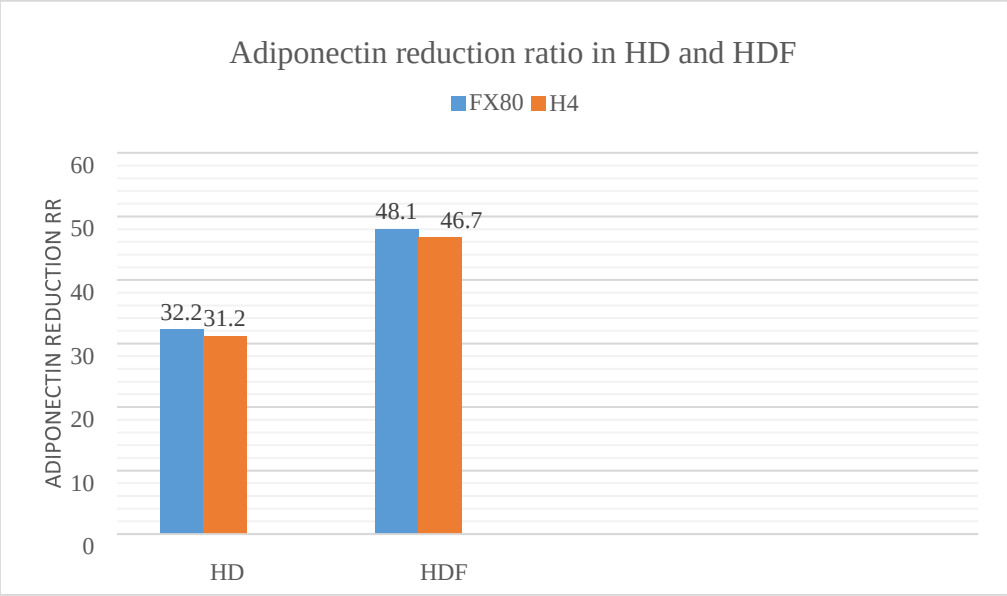

Figure (1): Adiponectin reduction ratio in HD and HDF using FX80 and H4

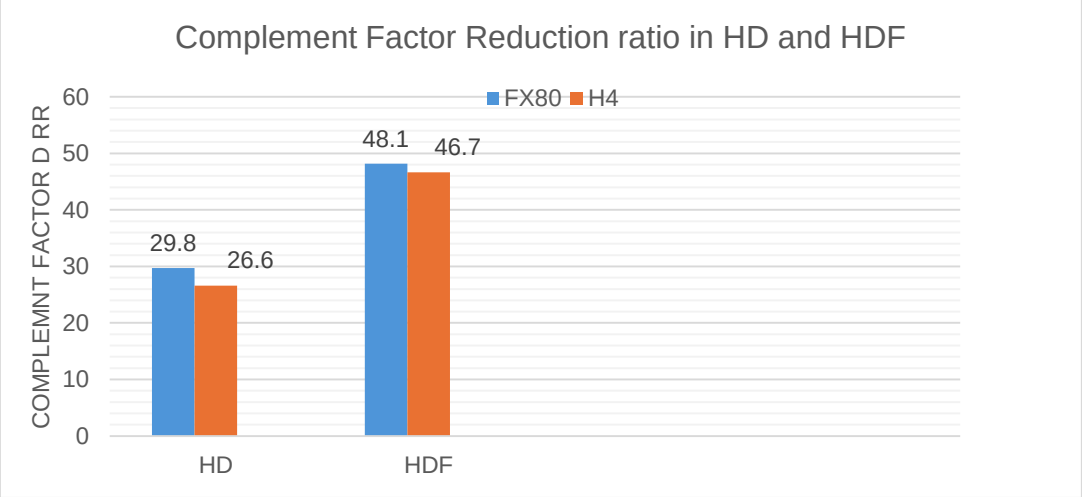

Figure (2): Complement factor D reduction ratio in HD and HDF using FX80 and H4

DISCUSSION

This study aims to compare the ability of high dose post dilution HDF to remove large middle molecules like Adiponectin and Complement Factor D to high flux dialysis using two different high flux dialysers.

Several studies explored the benefit of HDF over high flux HD on long term survival with conflicting results [14,15,16]. Recently High dose HDF more than 23 L convection volume has been proven to improve survival by reducing death from any cause. The survival benefit has been previously debated because of confounding according to indication. This has been refuted in the latest trial by **Blankestijn *et al.* [7],** which was randomised, and all patients involved were candidates for high dose HDF all the time.

There are two definitions of high dose HDF in different trials. High dosage HDF is defined as a convection volume of ≥23 L, whereas high-volume HDF aims for ≥21 L of replacement fluid per 1.73 m2 body surface area [17]. This study meets both definitions as shown in table1.

The survival superiority of HDF could be attributed to its ability to remove large middle molecules. High flux dialysers have a molecule size cut off 20 kDa which will limit the clearance of large middle molecules like Adiponectin (40 kDa) and Complement Factor D (24 kDa) during regular dialysis. HDF uses convection in combination with diffusive clearance to increase filtration of middle molecules.

Adiponectin has been linked to lower incidence of myocardial infarction in men with and without diabetes [9]. However, this association is not consistent in haemodialysis. Earlier studies by **Rao *et al.* [18] and Zoccali *et al.* [19]** proposed that greater levels of adiponectin are an inverse predictor of cardiovascular prognosis among patients with ESRD. More recent studies concluded that higher adiponectin is associated with a 3-fold higher death risk in HD patients independent of body composition and lipids [10].

Complement factor D is another large middle molecule, 24-kDa single-chain protein. It is the stage in the creation of C3 Convertase that limits the pace. It contributes to complement system dysregulation in ESRD patients since it is markedly higher in these individuals. It is well recognized that myocardial ischemia-reperfusion damage and endothelial dysfunction are related to complement activation and deposition [12].

The majority of studies assessed the ability of HDF to remove B2 microglobulin (11.8 kDa) in different dialysis modalities [20-22]. A few studies have assessed the removal of Adiponectin (40 kDa) and Complement Factor D (24 kDa). In this study reduction ratio of Adiponectin with HDF FX80 was 48.05 ±9.3 ng/ml and 46.7 ± 11.5 ng/ml with HDF H4. The Complement factor D reduction ratio with HD FX80 was 29.8 ±9.6 ng/ml and 48.29± 12.9 ng/ml with HDF FX80. This is in concordance with **Kirsch *et al.* [23]** who compared the performance of high flux dialysers during HD and HDF to medium cut off dialysers on large middle molecule clearance. Although we did not use medium cutoff dialysers, the results of complement factor D reduction ratio were similar to our findings with reduction ratios of 32.9% during high flux HD and 46.3% during HDF.

HDF offers better clearance of small molecules urea reduction ratio (URR) in HDF was 70.4 ± 6.8 mg/dl compared to HD only 65.1 ± 7 this agrees with **Kim *et al.* [24].**

There are several limitations in this study. Most of our patients were males. It is a study conducted on a relatively small number of patients. Urea reduction ratio was calculated around a single session of HD or HDF. It must be considered that the reduction of middle molecules after treatment is then ameliorated by rebound of middle molecules from the tissue to the plasma. There is also the possibility of adherence of the middle molecules to the dialyser membrane. The benefits of long-term reduction of Adiponectin and Complement factor D was not investigated in this study but might explain HDF related survival benefit and reduced mortality from any cause.

CONCLUSION

High-dose HDF showed better removal of adiponectin and complement factor D than HD, which further confirms its superior ability to remove middle molecules. No difference was observed between the use of two different high flux membranes FX80 and H4.

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Study registration:
The study was registered in Pan African Clinical Trial Registry database.
Registration number **PACTR202401461617766**.
Registration Date **(02/01/2024).** Retrospectively registered, https://pactr.samrc.ac.za/.

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