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Effect of hemodiafiltration versus high flux hemodialysis on reduction ratio of adiponectin and complement factor D as markers of dialysis adequacy

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ABSTRACT

Introduction: Dialysis therapy has significantly advanced due to innovations in dialyzer technology and hemodialysis (HD) techniques, leading to improved patient quality of life. The effectiveness of dialysis treatment can be assessed by evaluating the reduction ratio (RR) of middle-molecular-weight substances, such as adiponectin and complement factor D.

Objectives: To compare the clearance of adiponectin and complement factor D in patients undergoing hemodiafiltration (HDF) versus high-flux HD.

Patients and Methods: This prospective case-control study included 20 HD patients. Dialyzer efficacy were evaluated during a mid-week dialysis session. The RR of both adiponectin and complement factor D was assessed by 2 different HD modalities (HDF versus HD) using two different dialyzer (FX 80 and platinum H4), with washout period 2 weeks. Quality of life was assessed using Subjective Global Assessment (SGA) score.

Results: Adiponectin RR using HDF FX80 was 36.8 ± 3.2 ng/mL compared to 22.6 ± 3.8 ng/mL with HD FX80 ($P < 0.001$). Moreover, adiponectin RR using HDF H4 was 51.4 ± 4.3 ng/mL compared to 27.1 ± 1.9 ng/mL with HD H4 ($P < 0.001$). Complement factor D RR using HDF FX80 was 34.7 ± 2.1 pg/mL compared to 19.8 ± 2.8 pg/mL with HD FX80 ($P < 0.001$). furthermore, complement factor D RR using HDF H4 was 52.7 ± 5.3 pg/mL compared to 29.6 ± 3 pg/mL using HD H4 ($P < 0.001$).

Conclusion: We concluded that, HDF using H4 dialyzer offered better removal of adiponectin and complement factor D compared to high flux HD. A difference was observed between the two high-flux dialyzers used. We also found SGA score negatively correlated with serum albumin.

Implication for health policy/practice/research/medical education:
In a prospective case-control study on 20 hemodialysis (HD) patients, we found hemodiafiltration using H4 dialyzer offered better removal of adiponectin and complement factor D compared to high flux HD.

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Introduction

End-stage renal disease (ESRD) poses a major global health burden, contributing to elevated rates of morbidity and mortality (1). Uremic retention solutes, which accumulate due to impaired kidney function, have been systematically classified by the European Uremic Toxin (EUTox) Working Group into three distinct categories based on their physicochemical properties and dialyzability: Small water-soluble compounds (molecular weight <500 Da), Protein-bound uremic toxins, and Middle molecules (molecular weight >500 Da) (2).

Although renal replacement therapy, particularly dialysis, has advanced significantly in recent decades, patients undergoing conventional hemodialysis (HD) continue to experience substantial complications that negatively impact survival and quality of life (3). The primary objective of dialysis is the efficient clearance of uremic toxins; however, mortality rates among dialysis-dependent patients remain persistently high (1).

This elevated risk may be attributed to several factors, including the expanding dialysis population and the rising prevalence of comorbid conditions such as diabetes and hypertension, both of which are strongly associated with cardiovascular complications. Additionally, chronic

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inflammation—driven in part by the inadequate removal of middle- and large-molecular-weight uremic solutes—further exacerbates morbidity and mortality in this patient population (2).

Unlike conventional HD, hemodiafiltration (HDF) utilizes both diffusive and convective mechanisms to enhance the clearance of uremic toxins across a broader molecular weight spectrum, including both low- and high-molecular-weight solutes (4). Nevertheless, the implementation of HDF is associated with several challenges, such as the requirement for specialized equipment, a substantial volume of ultrapure replacement fluid, and the involvement of highly trained healthcare professionals (5).

It is well recognized that several 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 (6).

Adiponectin is a 30-kDa peptide hormone predominantly synthesized and secreted by adipose tissue, known for its anti-inflammatory and antiatherogenic properties (7). However, studies in HD patients have yielded conflicting results, with some reporting a paradoxical association between elevated adiponectin levels and increased mortality (8).

Due to its intermediate molecular weight, adiponectin is effectively eliminated through convective transport during dialysis. Consequently, it serves as a valuable biomarker for assessing the removal efficiency of middle- and large-molecular-weight solutes in renal replacement therapy. This utility stems from its accumulation in renal failure, optimal molecular size, and predominant clearance via convection (9).

Complement factor D, a 25-kDa serine protease, functions as the rate-limiting enzyme in the formation of C3 convertase within the alternative complement pathway. Patients with ESRD exhibit significantly elevated levels of this protein, leading to substantial complement system dysregulation. Notably, complement activation and subsequent protein deposition have been implicated in the pathogenesis of myocardial ischemia-reperfusion injury and endothelial dysfunction (10).

On the other hand, malnutrition represents a complex and widespread complication in ESRD patients undergoing HD, significantly contributing to adverse clinical outcomes. Key etiological factors include reduced dietary protein intake, anorexia, chronic inflammation, diminished residual kidney function, and suboptimal dialysis adequacy (11).

Meanwhile, the Subjective Global Assessment (SGA) is a validated clinical instrument for nutritional status evaluation, incorporating both patient history and physical examination parameters. In the present investigation, the SGA score will be employed to assess patient quality of life (12).

Objectives

This study aims to evaluate the comparative efficacy of HDF versus high-flux HD in clearing large middle molecules, specifically adiponectin and complement factor D, using two high-flux dialyzers (Platinum H 4 and FX 80) with its impact on quality of life using SGA score.

Patients and Methods

Study population and study design

This prospective case-control study was conducted at the Ain Shams university specialized hospital from March 2023 till March 2024.Our study population comprised 20 adult prevalent HD on 4 hours sessions thrice weekly patients. Patients with temporary dialysis catheters, active inflammation, infections, end stage organ failure and patients who were non-compliant on HD were excluded.

Patients underwent four different dialysis sessions in random order; HD with platinum H4 (HD H4), HD with FX80 (HD FX80), HDF with platinum H4 (HDF H4), HDF with FX80 (HDF FX80). Each session lasted four hours, with a blood flow rate (QB) of at least 300 mL/min. Sodium bicarbonate dialysate was used, and unfractionated heparin served as the anticoagulant. Treatments were performed on 5008S CorDiax machines. HDF sessions targeted a substitution volume >23 L, blood flow rate > 300 mL/min, and dialysate flow rate >500 mL/min.

Blood samples were collected from the arterial line at baseline and 30 seconds following a reduction in blood flow rate (Qb) to between 50 and 80 mL/min during a mid-week dialysis session. There was a two-week washout period between sessions. Blood samples for adiponectin, complement factor D, potassium, bicarbonate, and urea were withdrawn before and after each session, CBC, albumin, calcium, phosphate, and parathyroid hormone (PTH) levels were measured. All patients had full history and examination recorded, including the cause of ESRD, HD and HDF-related parameters (ultrafiltration volume, blood flow rate, body weight, convection volume, and substitution volume) were documented, additionally, the quality of life of these patients was assessed using the SGA score.

Dialyzer and dialysis conditions

We compared the two dialyzers we frequently use in our unit. Platinum H4 dialyzer is made of enhanced micro undulated polysulfone hollow fibers with steam sterilization and 1.8m2 surface area and compared to FX80 dialyzer, made of helixone membrane with housing material polypropylene with steam sterilization and 1.8 m^2 surface area (Table 1).

Laboratory measurements

The following laboratory tests were done at baseline using commercially available kits: complete blood count (CBC), blood urea nitrogen (BUN), serum creatinine, sodium,

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 (11.8 kD)	0.8	0.85
Albumin (66.5 kD)	0.001	<0.001
UF coefficient (mL/h/mm Hg)	53	58
KoA urea (mL/min^2)	1429	1394
Sterilization	Steam	Steam

B2m: Beta 2 microglobulin; UF: Ultrafiltration; KoA: mass transfer area coefficient.

potassium, calcium, phosphorus, PTH levels, ferritin, iron, total iron binding capacity, and serum albumin. Additionally, serum adiponectin and complement factor D levels were measured. All blood samples were taken and transported to testing facilities under standardized circumstances.

Serum adiponectin and complement factor D levels were measured before and after each patient's treatment with two HD modalities; high-flux hemodialysis (HF-HD) and post-dilution online hemodiafiltration (OL-HDF). Blood samples were collected from the arterial line at both the beginning and end of each dialysis session. After collection, the samples were allowed to rest at room temperature (18-25 °C) for 10 minutes to clot, followed by centrifugation at 1000 revolutions per minute (rpm) for 20 minutes. The supernatant was then carefully removed. If precipitation was observed, the centrifugation process was repeated.

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 the quantitative detection of ADP in human blood, plasma, tissue homogenates, cell lysate, cell culture supernates, and other biological fluids. The microtiter plate provided in this kit has been pre-coated with an antibody specific to ADP. The minimum detectable dose of ADP is typically less than 0.65 ng/mL.

Complement factor D levels were measured using the DEVELOP Human Complement Factor D (CFD) ELISA Kit (Catalog No: DL-CFD-Hu). This kit is a sandwich enzyme immunoassay designed for the quantitative detection of complement factor D in human blood, plasma, tissue homogenates, cell lysates, cell culture supernatants, and other biological fluids. The microtiter plate included in this kit is pre-coated with an antibody specific to CFD. The assay's minimum detectable dose of CFD is typically less than 0.137 ng/mL.

Calculations

The post-dialysis concentrations of complement factor D and adiponectin were adjusted for hemoconcentration following the method described by Bergström and Wehle (13).

$$A\ post\ C. = \frac{A\ post}{(1 + \frac{\triangle\ BW}{0.2\ x\ BW post})}$$

which A post C shows adiponectin level post session after correction for net ultrafiltration (UF); A post is adiponectin post-session; BW is the body weight; and BW post is the body weight after ultrafiltration.

$$Factor\ D\ post\ C. = \frac{Factor\ D\ post}{(1 + \frac{\triangle\ BW}{0.2\ x\ BW post})}$$

which factor D post c shows Complement factor D post session after correction for net UF; Factor D post is factor D post-session; BW is body weight; and BW post is the body weight after ultrafiltration.

The following equation is used to calculate the reduction ratio (RR):

$$RR = \frac{A\ Pre - A\ post}{A\ Pre}\ x\ 100$$

which RR is reduction ratio; A post is adiponectin post treatment; and A pre is adiponectin pre-treatment. Reduction percentages were calculated by multiplying the reduction ratio by 100%.

$$RR = \frac{Factor\ D\ Pre - Factor\ D\ post}{Factor\ D\ Pre}\ x\ 100$$

which RR is reduction ratio; Factor D post is factor D post-treatment; and Factor D pre is factor D pretreatment. The reduction ratio was multiplied by 100% to determine the reduction percentages.

SGA score

The SGA score comprises seven evaluation components: weight change, dietary intake, gastrointestinal symptoms, functional status, metabolic demands, fat stores, muscle stores, and the presence of edema. The scoring system is as follows: a score of 7-14 indicates well-nourished status,

15-28 denotes mild to moderate malnutrition, and a score greater than 29 indicates severe malnutrition.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS Statistics software (version 28.0, IBM Corp., Chicago, USA, 2021). Qualitative data were presented as frequencies and percentages. Quantitative data were assessed for normality using the Shapiro-Wilk test and subsequently described as mean ± standard deviation (SD), along with the minimum and maximum values. Comparisons were made using the paired t-test for two paired variables and repeated measures analysis of variance (RMANOVA) for four paired variables. Pearson's correlation coefficient was used to assess relationships between variables. Post hoc comparisons were conducted using the Bonferroni test. Statistical significance was defined as a *P* value ≤ 0.05; values greater than 0.05 were considered non-significant.

Results

All patients were assessed for the RR of adiponectin and complement factor D by 2 different HD modalities using two different dialyzers (FX 80 and platinum H4), with a washout period of two weeks between them.

- Modality A: high flux HD once with FX 80 and once with platinum H4
- Modality B: post-dilution online HDF with substitution goal ≥ 20 L, blood flow rate ≥ 300 ml/min) once with FX 80 and once with platinum H4.

Regarding laboratory investigations, mean hemoglobin level was 10.9 ± 1.2 g/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). Urea reduction ratio (URR) in HDF was 70.4 ± 6.8 compared to HD only 65.1±7.

Mean dry weight was 84.8±17.3 kg (Table 2). Mean ultrafiltration volume was 2.7±0.83 L. HDF parameters were: post-dilution substitution volume was an average of 21.6±0.8 L, Blood flow rate average was 352±8 mL/min, and the mean convection volume was 24.3±1.1 L.

Table 3 and Figure 1 show no significant differences between the study groups regarding pre-dialysis serum adiponectin levels. The serum adiponectin RR was highest in HDF-platinum H4, followed by HDF-FX80, then HD-platinum H4 and lowest in HD-FX80. The differences were significant between each group.

Table 4 and Figure 2 showed no significant differences between the study groups regarding pre dialysis complement factor D. The serum complement factor D RR was highest in HDF-Platinum H4, followed by HDF-FX80, then HD-Platinum H4 and lowest in HD-FX80. The differences were significant between each group.

There were no significant differences between the study groups regarding pre-dialysis serum potassium levels.

Table 2. Demographic characteristics of the studied groups

Characteristics		Mean ± SD	Range
Age (years)		50.5±10.4	29.0–68.0
Weight (kg)		84.8±17.3	51.0–123.0
Height (m)		1.7±0.1	1.6–1.8
Body mass index (kg/m²)		29.0±5.1	19.9–41.1
SGA score		11.8±3.0	7.0–17.0
		n	%
Gender	Male	18	90.0
	Female	2	10.0

SGA: Subjective Global Assessment.

Table 3. Serum adiponectin between the studied groups

Time	Group	Mean±SD	Range (ng/mL)	*P* value
Pre dialysis	HDF-FX80	30.3±18.3	8.2–68.0	0.999
	HDF-platinum H4	30.4±22.3	4.0–92.0	
	HD-FX80	30.3±24.8	7.0–81.0	
	HD-platinum H4	29.7±20.2	7.0–77.0	
Post dialysis	HDF-FX80	22.7±17.9ab	3.0–76.5	0.038*
	HDF-platinum H4	16.7±9.2a	5.0–36.0	
	HD-FX80	27.1±21.9b	7.0–72.0	
	HD-platinum H4	25.0±17.4ab	6.0–69.0	
C-post dialysis	HDF-FX80	19.5±15.7ab	2.5–68.9	0.032*
	HDF-platinum H4	14.4±8.1a	4.4–31.5	
	HD-FX80	23.5±19.4b	5.9–63.1	
	HD-platinum H4	21.6±15.0ab	5.3–58.3	
Reduction ratio	HDF-FX80	36.8±3.2a	25.1–39.9	<0.001*
	HDF-platinum H4	51.4±4.3b	38.3–55.0	
	HD-FX80	22.6±3.8c	15.5–28.4	
	HD-platinum H4	27.6±1.9d	23.8–29.9	

C-post dialysis; Corrected post dialysis concentration.
Total = 20. *Significant. Homogeneous groups were assigned the same symbol based on the post hoc Bonferroni test.

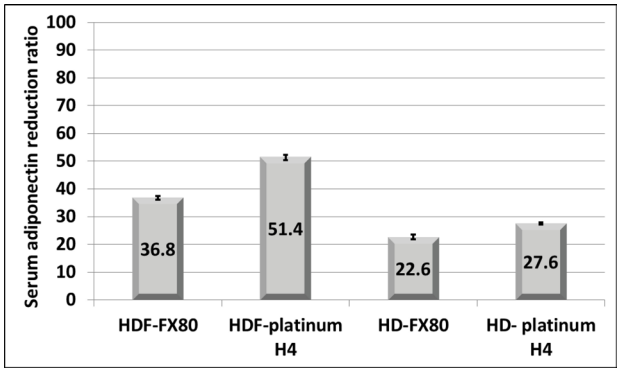

Figure 1. Serum adiponectin reduction ratio.

Table 4. Serum complement factor D between the studied groups

Time	Group	Mean±SD	Range (ng/mL)	*P* value
Pre dialysis	HDF-FX80	37.9±15.5	16.0–64.0	0.982
	HDF-platinum H4	38.7±15.6	18.0–70.0	
	HD-FX80	38.4±16.8	13.0–70.0	
	HD-platinum H4	37.5±14.7	17.0–60.0	
Post dialysis	HDF-FX80	28.6±11.7a	12.0–46.0	<0.001*
	HDF-platinum H4	21.7±10.1b	9.0–41.0	
	HD-FX80	35.8±15.6a	11.0–63.0	
	HD-platinum H4	30.8±12.6a	14.0–50.0	
C-post dialysis	HDF-FX80	24.6±9.9a	10.6–41.0	<0.001*
	HDF-platinum H4	18.6±8.5b	8.0–35.2	
	HD-FX80	30.7±13.5a	9.9–57.4	
	HD-platinum H4	26.3±10.2a	12.3–41.8	
Reduction ratio	HDF-FX80	34.7±2.1a	30.5–37.5	<0.001*
	HDF-platinum H4	52.6±5.3b	43.4–59.8	
	HD-FX80	19.8±2.8c	14.5–24.1	
	HD-platinum H4	29.6±3.0d	23.0–34.1	

C-post dialysis; Corrected post dialysis concentration.
Total = 20. *Significant. Homogeneous groups were assigned the same symbol based on the post hoc Bonferroni test.

Serum potassium significantly decreased in all study groups; however, the differences were non-significant between each group, as shown in Figure 3. Additionally, there were no significant differences between the study groups regarding pre-dialysis serum HCO_3 levels. Furthermore, serum HCO3 was significantly elevated in all study groups; however, the differences were non-significant between each group.

Discussion

Renal replacement therapy has undergone significant advancements since its introduction, with improvements in dialyzer technology and HD modalities. These innovations have reduced complications associated with renal replacement therapy and improved patient outcomes. Dialysis efficacy assessment commonly involves measurement of RRs for middle-molecular-weight compounds, including adiponectin and complement factor D, which serve as clinically relevant biomarkers (14).

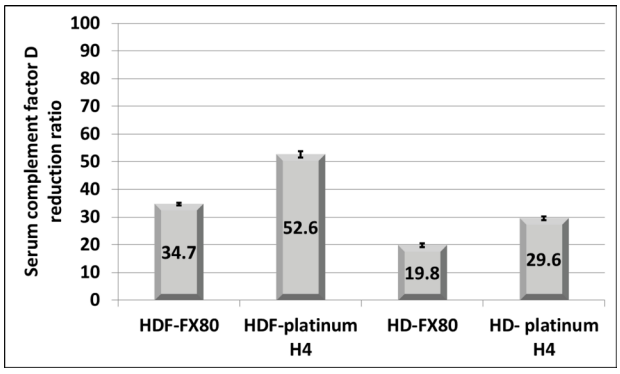

Figure 2. Serum complement factor D reduction ratio.

Several studies investigated the benefits of HDF versus high-flux HD concerning long-term survival with conflicting results (15-17). Recently high dose HDF (more than 23 L convection volume) has been shown to improve survival by reducing mortality from any cause. The survival benefit has been previously debated because of confounding factors related to indication. But this was refuted in the latest trial by which was randomized, and all patients were candidates for HDF all the time (18).

Two distinct definitions of high-dose HDF have been employed across various trials. High-dose HDF is characterized by a convection volume of ≥23 L, whereas high-volume HDF targets ≥21 L of replacement fluid per 1.73 m^2 of body surface area (14). The survival advantage associated with HDF may be attributed to its enhanced ability to eliminate large middle molecules. High-flux dialyzers have a molecular size cutoff of 20 kDa, which limits the clearance of larger middle molecules such as adiponectin (30 kDa) and CFD (24 kDa) during standard dialysis. In contrast, HDF combines convection with diffusive clearance, facilitating improved filtration of these middle molecules.

Adiponectin has the ability to lower incidence of

myocardial infarction in men with and without diabetes (7). However, this association is not consistent in HD. Earlier studies by Rao et al (19) and Zoccali et al (20) suggested that elevated levels of adiponectin are inversely correlated with cardiovascular prognosis in patients with end-stage renal disease. More recent research, however, has found that higher adiponectin levels are associated with a threefold increased risk of mortality in HD patients, independent of body composition and lipid levels (8).

Complement factor D is another large middle molecule, 24-kDa single-chain protein. It plays a role in the creation of C3 Convertase, which regulates the pace of complement system activation. It contributes to complement system dysregulation in ESRD patients since it is markedly higher in these individuals. Complement activation and deposition are associated with myocardial ischemia-reperfusion damage and endothelial dysfunction (21).

Most studies have assessed the ability of HDF to remove B2 microglobulin (11.8 kDa) in different dialysis modalities (20-22). Few studies have assessed the removal of Adiponectin (30 kDa) and Complement Factor D (24 kDa).

Our analysis revealed comparable baseline pre-dialysis serum adiponectin concentrations across all study cohorts. Serum adiponectin relative risk (RR) was highest in HDF-Platinum H4 (51.4 ± 4.3b), followed by HDF-FX80 (36.1 ± 3.2a), then HD-Platinum H4 (27.6 ± 1.9d), and lowest in HD-FX80 (22.6 ± 3.8c). The differences were significant between all groups, with a P value < 0.001, as shown in Table 4.

Regarding serum complement factor D, Table 5 shows no significant differences in pre-dialysis levels among the study groups. The serum Complement Factor D RR was highest in HDF-Platinum H4 (52.6±5.3b), followed by HDF-FX80 (34.7±2.1a), then HD-Platinum H4 (29.6±3.0d) and lowest in HD-FX80 (19.8±2.1a) the differences were significant between all groups P value <0.001. This is in concordance with (22), who compared the performance of high flux dialyzers during HD and HDF to medium cut-off dialyzers on large middle molecule clearance. Although we did not use medium cut-off dialyzers, the results of complement factor D RR were similar to our findings with RRs of 32.9% during high flux HD and 46.3% during HDF.

Our study compared the RRs of adiponectin and complement factor D between high-flux HD and HDF. The results demonstrated significantly greater clearance of both biomarkers following HDF treatment compared to conventional high-flux HD. When comparing the two high flux dialyzers, Adiponectin RR using HD FX80 was 22.6± 9 ng/mL compared to HD H4 27.1 ±1.9 ng/mL. Complement D RR was HD FX80 19.8 ± 2.8 pg/mL compared to 29.6±3 pg/mL HD H4, indicating that plat H4 was better than FX80.

For adiponectin RR, HDF FX80 was 36.1± 3.2 ng/mL compared to 51.4± 11.5 ng/mL HDF H4. For complement D RR, HDF FX80 was 34.7 ± 2.9 pg/mL compared to 52.6± 5.3 pg/mL for HDF H4, indicating that plat H4 was superior to FX80.

Regarding blood urea, the study groups showed comparable baseline pre-dialysis serum urea levels (P > 0.05). However, both post-dialysis and corrected post-dialysis urea concentrations were significantly lower in the HDF group compared to high-flux HD (P < 0.05). This enhanced clearance was reflected in a significantly higher URR for HDF (70.4 ± 6.8%) versus HD (65.1 ± 7.0%). These results demonstrate HDF's superior efficiency in small molecule clearance, consistent with previous findings (23).

Malnutrition is a complex, multifactorial, and widespread issue among maintenance HD patients, contributing to increased morbidity and mortality rates (11). The malnutrition observed in those patients is driven by various factors, including insufficient protein and calorie intake, anorexia, inflammation, loss of residual renal function, and inadequate dialysis.

Our study aimed at assessing the nutritional status of chronic kidney disease patients using the SGA. The SGA score is a clinical tool that evaluates nutritional status based on historical and physical examination findings (12). The SGA grading system comprises seven assessment items: weight change, dietary intake, gastrointestinal symptoms, functional status, metabolic demands, fat stores, muscle stores, and the presence of edema. The mean SGA score in our study was 11.8±3.0. 14 patients were well-nourished with scores ranging from 7 to 14, while the remaining patients were mildly to moderately malnourished, as their scores ranged from 14 to 20. None were severely malnourished.

Additionally, in our study no correlation between SGA scores and pre-dialysis labs was detected, except for a significant negative correlation between SGA and baseline albumin (P < 0.001) (11).

Conclusion

Adiponectin and complement factor D can be used as markers of dialysis adequacy. We concluded that HDF achieves better removal of adiponectin and complement factor D compared to HD, which further confirms its superior ability to remove middle molecules. A difference was noted in the performance of the two different high-flux membranes used FX80 and ptinum H4, with a greater reduction noted for the platinum H4 membrane.

Limitations of the study

While our study provides valuable insight regarding the utilization of adiponectin and CFD as markers of dialysis adequacy, as well as the efficacy of different dialysis modalities and dialyzers, some limitations should be taken into account. For instance, a relatively small number of patients were studied, most of which were males. Also, URR was calculated for a single session of HD or HDF. In

addition, it must be noted that the reduction of middle molecules after treatment may be offset by the rebound of these molecules from tissue to plasma. Last but not least, there is also the possibility of adherence of middle molecules to the dialyzer membrane.

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Authors' contributions

Conceptualization: Hesham El-Sayed and Magdy El-Sharkawy.
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Validation: Ahmed Tawafik and Lamis Khedr.
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Writing–original draft: Mahmoud Fayez.
Writing–review & editing: Ahmed Tawafik and Lamis Khedr.

Conflicts of interest

The authors declare that there are no conflicts of interest associated with the publication of this paper.

Data availability statement

Data generated in this study is available from the corresponding author upon reasonable request.

Ethical issues

The research was conducted in accordance with the principles outlined in the Declaration of Helsinki. The Ethics Committee of the Faculty of Medicine at Ain Shams University (reference number FWA 000017585) approved this study. Accordingly, written informed consent was taken from all participants before any intervention. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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