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Safwat Farrag Ahmed
Department of Nephrology and internal Medicine, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt

Alsayed Mohamed Rashed
Department of Nephrology and internal Medicine, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt

Mohammad Assayed Abo-Ghabsha
Department of Clinical pathology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt.

Ahmed Kamal Hassanin Mansour
Department of Nephrology and internal Medicine, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt, ahmedkamal1436@gmail.com

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ORIGINAL ARTICLE

Cystatin C as a Marker of Hemodialysis Adequacy in Adults

Safwat Farrag [a], Alsayed Rashed [a], Mohammad Abo-Ghabsha [b], Ahmed Kamal [a,*]

[a] Department of Nephrology and Internal Medicine, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt
[b] Department of Clinical Pathology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: **Cystatin C (CyC) level in plasma is an emerging measure for evaluating kidney function. However, its usefulness in determining how well hemodialysis is working for individuals with end-stage renal disease has not yet been proven.**

Aim and objectives: **Aim of the study was to evaluate cystatin C as a marker of adequacy of hemodialysis (HD) in adults.**

Subjects and methods: **This study started between first of May 2022 and first of August 2022 and was conducted on 90 patients; 45 of them at Al-Hussain university hospital in Cairo and 45 of them at Arab Organization for Industrialization hospital in Cairo, all patients were selected from hemodialysis units in both hospitals.**

Results: **There was a substantial decrease in both groups (p 0.001) when the mean values of serum urea, cystatin C, urea reduction ratio (URR), cystatin C reduction ratio (CCRR), and Kt/V were compared before and after the dialysis session. Our findings demonstrated that pre-dialytic mean blood levels of CyC and urea in our adult patients undergoing high-flux hemodialysis (HFH) were significantly lower than those undergoing low-flux hemodialysis (LFH).**

Conclusion: **Our findings indicated improved renal parameters as well as higher MM clearance. In our study, the effectiveness of the CCRR is assessed as a measure of the sufficiency of HD sessions for individuals on HFH. We also discovered that because CyC was not considerably eliminated in LFH, it cannot be employed as a measure of toxin clearance.**

Keywords: Cystatin C, End stage renal disease, Hemodialysis, Marker

1. Introduction

The kidney disease: enhancing global outcomes According to a recent consensus conference, end-stage renal disease (ESRD) is characterised by an estimated glomerular filtration rate of less than 15 mL/min/1.73 m^2 or by the need for dialysis.[1]

Cystatin C, a 13 kD non-glycosylated simple protein that acts as an endogenous marker for tracking GFR, is continuously produced and secreted by all nucleated cells. This endogenous serum biological marker is freely filtered by the glomerulus due to its cationic nature. It differs from creatinine in that it possesses extra features that are present at steady plasma concentrations, is not secreted by tubular cells, and is less affected by non-renal elements like gender, age, muscle mass, and analytically interfering chemicals.[2]

The build-up of uremic toxins in the body, which affects many tissues and organs, including the cardiovascular system, is one of the principal effects of the loss of renal function. There is production, degradation, and excretion of uremic toxins. Their biological effects also depend on their cytoplasmic distribution and whether or not other substances are suppressing or promoting them.[3]

According to the European Uremic Toxin Work Group (EUTox), the three groups of uremic toxins described below can be distinguished based on their physicochemical properties and how they behave

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* Corresponding author at: Department of Nephrology and Internal Medicine, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt.
E-mail address: ahmedkamal1436@gmail.com (A. Kamal).

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during dialysis: Small-water soluble substances (molecular weight 500 Da or less), such as creatinine and urea, medium-water soluble substances (peptides with a molecular weight >500 Da), such as cystatin-C and beta2-microglobulin, and protein-bound uremic toxins (PBUTs), Only dialysis membranes with a large pore size are capable of eliminating substances like phenols and indoles.

Adequacy of dialysis is traditionally measured by urea reduction ratio (URR) and Kt/V (K is the Urea clearance, t is time of dialysis and V is volume of distribution of patient). The objective Kt/V for each session should be 1.4 in accordance with the Kidney Disease Initiative Global Outcome (KDIGO) standards. The study's objective was to evaluate how individuals responded to hemodialysis using cystatin-C.

1.1. Patients and methods

This study started between first of May 2022 and first of August 2022 and was conducted on 90 patients; 45 of them at Al-Hussain university hospital in Cairo and 45 of them at Arab Organization for Industrialization hospital in Cairo, all patients was selected from hemodialysis units in both hospitals.

Inclusion criteria included patients between 18 and 70 years of age and all patients suffered from end-stage renal disease (ESRD) and on regular hemodialysis for at least 3 months.

Exclusion criteria included; autoimmune diseases, the presence of active infections (clinically manifested as fever, cough, nausea, vomiting, diarrhea, etc.), non-compliant patients and patients who were treated by medications that could affect their hemoglobin (Hb) level such as immune-suppressants.

The study was performed on ninety patients at hemodialysis units of Al-Hussain hospital in Cairo and Arab Organization for Industrialization in Cairo. Ethical committee regulations (Med_235Med-Research_Cystatin C/Hemodialysis Adequacy-Adults_00000235) faculty of medicine Al-Azhar university and a written informed consent was taken from the patients with explanation of the procedure's possible hazards. All patients were receiving hemodialysis three times weekly due to end stage renal disease (ESRD).

A total of 90 patients were divided into two groups: group A, who utilised high-flux polysulfone filters (FX80 classix and FX60 according to body surface area), and group B, who used low-flux filters (Polyflux according to surface area). Each patient received a Fresenius HD machine 4008S. (Fresenius Medical Care Co.).

Ninety hemodialysis patients with end-stage renal disease underwent the following workup: complete medical history collecting and evaluation. Complete blood count (C.B.C.) using Sysmex automated hematology analyzer according to (Wallace H. Coulter in 1953) who used the Coulter principle (electrical impedance) in counting blood cells and determine their sizes. Chemistry experiments utilising a Mindray automated chemical analyzer include measuring serum creatinine using the Patton and Crouch-recommended alkaline picrate method and measuring the creatinine-picrate complex at 492 nm (1977). Using the urease-colorimetric approach, serum urea was calculated based on the Fenton reaction with the di azine chromogen. Bowers and Wong, 1980, serum calcium was assayed in clear supernatants of the tissue homogenates according to the procedure suggested by Babson and Babson, (1973), serum phosphorus and serum Parathyroid hormone (PTH) was measured using immunoradiometric assay. Serum Cystatin -C was assayed at the beginning and at the end of the study using Mispa-i2 semi-automated specific protein analyzer according to nephelometry method. Urea reduction ratio (URR) measurement by computerized method according to equation (100)*(1-Ui/Uo) where Ui and Uo represent post-dialysis and pre-dialysis serum urea levels. Cystatin-c reduction ratio (CCRR) measurement by computerized method according to the same equation of URR. Single pool Kt/V by computerized method according to Daugirdas equation.

1.2. Statistical methods

With the help of the Statistical Package for Social Sciences (SPSS) version 27 for Windows, the data was coded, processed, and analysed (IBM SPSS Inc, Chicago, IL, USA). The Shapiro Walk test was employed to determine whether the data distribution was normal. Frequencies and relative percentages were employed to depict qualitative data. The qualitative variables' degree of difference was assessed using the chi square test, as shown in the example (2). Non-parametric quantitative data were expressed as median, whereas parametric quantitative data were expressed as mean SD (Standard Deviation) (range). The Mann Whitney *U* test was used to compare parametric data with non-normally distributed variables, while the independent samples *t*-test was used to compare parametric data with variables that were regularly distributed (non-

parametric data). To compare two dependent groups of normally distributed variables, paired samples *t*-test was utilised (parametric data). With non-parametric quantitative data, Pearson's/correlation Spearman's was utilised to examine the relationship between two variables.

2. Results

The patients in this study are ESRD patients and they are on maintenance hemodialysis, their ages between 18 and 70 years old. All patients had a GFR <15/ml/min./m^2. 45 patients (group A) (50%) were on high-flux hemodialysis (HFH) and the other 45 patients (group B) (50%) were on low-flux hemodialysis (LFH).

The differences in the efficiency of dialysis using high-flux compared to low-flux dialyzers expressed as RRs and Kt/V are shown in (Table 1).

There were no statistically significant correlations between-group differences for the demographic characteristics and co-morbid conditions (such as diabetes and hypertension) are shown in (Table 1), calcium and PTH (Table 2).

Analysis of Cystatin C level (Basal and after 3 months) in the two study groups is shown in (Table 3).

Comparisons of the mean levels of the measures of serum urea, cystatin c, URR, CCRR and Kt/V before and after the dialysis session revealed that in both groups there was a significant decline ($P < 0.001$) (Table 4).

Table 1. Analysis of demographic data in the two study groups.

	Group A [High-flux dialyzer] ($N = 45$)	Group B [Low-flux dialyzer] ($N = 45$)	Test of significance	*P* value
Age (Years)	**52.87 ± 7.18**	**52.02 ± 7.01**	t = 0.565	0.574
Sex				
Male	**23 (51.1%)**	**20 (44.4%)**	$\chi 2 = 0.401$	0.527
Female	**22 (48.9%)**	**25 (55.6%)**		
Residence				
Urban	**15 (33.3%)**	**18 (40%)**	$\chi 2 = 0.431$	0.512
Rural	**30 (66.7%)**	**27 (60%)**		
Diabetes mellitus	**16 (35.6%)**	**17 (37.8%)**	$\chi 2 = 0.048$	0.827
Hypertension	**15 (33.3%)**	**14 (31.1%)**	$\chi 2 = 0.051$	0.822

t, Independent samples *t*-test; $\chi 2$, Chi-square test.

Table 2. Analysis of serum level of calcium, phosphorous and PTH in the two study groups.

	Group A [High-flux dialyzer] ($N = 45$)	Group B [Low-flux dialyzer] ($N = 45$)	Test of significance	*P* value
Calcium (mg/dl)	8.65 ± 0.41	8.45 ± 0.59	t = 1.898	0.061
Phosphorous (mg/dl)	4.63 ± 1.10	5.57 ± 1.70	t = - 3.084	0.003*
PTH (Pg/ml)	217 (115–547)	225 (60–614)	z = −0.016	0.987

t, Independent samples *t*-test; z, Mann-Whitney *U* test.
*: Statistically significant ($P < 0.05$).

Table 3. Analysis of Cystatin C level (Basal and after 3 months) in the two study groups.

	Group A [High-flux dialyzer] ($N = 45$)	Group B [Low-flux dialyzer] ($N = 45$)	Test of significance	*P* value
Cystatin C level before treatment (mg/L)	24.64 ± 2.97	24.42 ± 3.03	t = 0.351	0.726
Cystatin C level after treatment (mg/L)	1.52 ± 0.12	10.53 ± 0.55	t = −108.095	<0.001*
Mean percent of change	93.74 ± 0.79	56.34 ± 5.01	t = 49.477	<0.001*
P1 (Paired samples *t*-test)	<0.001*	<0.001*		

Table 4. Analysis of URR, serum creatinine, CCRR and Kt/V in the two study groups.

	Group A [High-flux dialyzer] ($N = 45$)	Group B [Low-flux dialyzer] ($N = 45$)	Test of significance	*P* value
URR	72.44 ± 4.15	66.98 ± 4.10	t = 6.282	<0.001*
Serum creatinine (mg/dl)	10.97 ± 3.09	10.66 ± 2.44	t = 0.527	0.600
CCRR	93.74 ± 0.80	56.34 ± 5.01	t = 49.457	<0.001*
Kt/V	1.53 ± 0.19	1.31 ± 0.13	t = 6.364	<0.001*

Table 5. Correlation between basal Cystatin C level with clinical and laboratory data in the cases of group A.

	Basal Cystatin C level
Age	
R	0.225
P	0.137
Calcium	
R	0.109
P	0.476
Phosphorous	
R	0.125
P	0.415
PTH	
R	0.016
P	0.916
UREA (Basal)	
R	−0.014
P	0.929
URR	
R	−0.011
P	0.945
Creatinine	
R	0.423
P	0.004*
CCRR	
R	0.808
P	<0.001*
Kt/V	
R	0.057
P	0.711

Table 6. Correlation between basal Cystatin C level with clinical and laboratory data in the cases of group B.

	Basal Cystatin C level
Age	
R	−0.038
P	0.804
Ca	
R	−0.188
P	0.215
Ph	
R	−0.020
P	0.897
PTH	
R	0.190
P	0.211
UREA (Basal)	
R	0.039
P	0.800
URR	
R	0.282
P	0.060
Creatinine	
R	−0.062
P	0.685
CCRR	
R	0.913
P	<0.001*
Kt/V	
R	0.244
P	0.107

r: Pearson's/spearman's correlation.
*: Statistically significant ($P \leq 0.05$).

The Correlation between basal Cystatin C level with clinical and laboratory data in the cases of HFH group and LFH group were studied and shown in (Tables 5, 6).

3. Discussion

The objectives of HD include the elimination of extra fluid as well as the efficient and secure clearance of solutes, including MMs, protein-bound solutes, and tiny plasma solutes. According to Liabeuf and colleagues,[4] MMs build up in the bodies of HD patients and increase their risk of cardiovascular disease and mortality.[5]

In order to evaluate the effectiveness of maintenance HD in ESRD patients, we looked into CyC and its RR as biomarkers. The effectiveness of low-flux and high-flux dialyzers was also contrasted in a variety of patients. There were no ESRD cause between-group differences that were statistically significant, demographics, co-morbid illnesses (including diabetes and hypertension), dialysis duration, type of vascular access, creatinine, calcium, nor PTH levels. When the mean measures of serum urea, cystatin C, URR, CCRR, and Kt/V were compared before and after the dialysis session, there was a significant decrease in both groups (p 0.001). According to our research, adult patients on HFH had significantly lower pre-dialytic mean blood levels of CyC and urea than those in patients on LFH. The CCRR, URR, and Kt/V were significantly different between the HFH group and the LFH group. These discoveries are reliable with past investigations that showed MMs as well as little subatomic solutes like urea and creatinine might be taken out more effectively by high-motion dialyzers than by low-transition dialyzers.[5]

Our outcomes showed that the CCRR, URR, and Kt/V of the HFH bunch were essentially higher than those of the LFH bunch. These outcomes were additionally upheld by past trials.[6]

A measurably huge expansion in the CCRR was seen in a concentrate by Liabeuf and partners in grown-up patients on HFH. These scientists arrived to the conclusion that high-flux dialyzers are effective at removing MMs and that CyC can be used to replace conventional markers as an essential dialysis adequacy measure. Indicators of small- and middle-molecule uremic toxin clearance, as well as their long-term consequences on clinical outcomes, seem to be CyC levels in HFH patients. The results of numerous studies that examined CyC in HFH lend credence to this discovery.[7]

Our results, which were in line with those of other studies, showed that CyC cannot be used to gauge

how much dialysis is being received by patients using low-flux dialyzers.[8]

Our findings for blood urea and creatinine levels were supported by other studies examining the relationship between serum CyC, a novel marker, and serum urea and creatinine, two conventional kidney markers.[6]

Reduction ratios (RRs) and Kt/V are measurements of the efficiency of high-flux vs low-flux dialyzers for dialysis. In the situations of the HFH group and LFH group, investigations were made into the relationship between the baseline Cystatin C level and clinical and laboratory data. Basal cystatin C, creatinine, and CCRR all showed a significant association in the HFH group. Basal cystatin C was strongly related with CCRR in the LFH group.

4. Conclusion

Our results showed better renal parameters, also our results showed increased MM clearance. In our study, the efficacy of the CCRR as a metric of HD session efficacy for those on HFH was evaluated. We also learned that CyC, which was not completely removed in LFH, cannot be employed as a measure of toxin clearance.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

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Conflicts of interest

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References

1. Zhang Z, Yang T, Li Y, Li J, Yang Q, Wang L, Jiang L, Su B. Effects of expanded hemodialysis with medium cut-off membranes on maintenance hemodialysis patients: a review. *Membranes*. 2022;12:253. https://doi.org/10.3390/membranes12030253.
2. Tapper M, McGrowder DA, Dilworth L, Soyibo A. 2021.
3. Cunha RSD, Azevedo CAB, Falconi CA, Ruiz FF, Liabeuf S, Carneiro-Ramos MS, Stinghen AEM. The interplay between uremic toxins and albumin, membrane transporters and drug interaction. *Toxins*. 2022;14:177. https://doi.org/10.3390/toxins14030177.
4. Fatina I, Abbass A, Azza MO, Hafez MB, Mohamed F, Dalia H, et al. Levels of cystatin C in low- and high-flux hemodialysis in children with end-stage renal disease. *Pediatr Nephrol*. Sept. 2017;32(9). https://doi.org/10.1007/s00467-017-3661-0.
5. Liabeuf S, Lenglet A, Maheshwari KU, Santhi S, Malar RJ. Cystatin C: an alternative dialysis adequacy marker in high flux hemodialysis. *Indian J Nephrol*. 2015;25:143–145.
6. Micle O, Vicas SI, Ratiu I, Vicas L, Muresan M, Cystatin C. A low molecular weight protein in chronic renal failure. *FARMACIA*. 2015;63:872–876.
7. Huang SH, Filler G, Yasin A, Lindsay RM. Cystatin C reduction ratio depends on normalized blood liters processed and fluid removal during hemodialysis. *Clin J Am Soc Nephrol*. 2011;6:319–325.
8. Mateen FE, Ahmad S, Elahi I, Anees M. Comparison between different methods of calculating Kt/V as the marker of adequacy of dialysis. *Pakistan J Med Sci*. 2022;38:167–171.