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Mohamed Nabil Raafat

Professor of Internal Medicine and Clinical Immunology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Ahmed Alaa Eldin Ahmed Saad

Professor of Internal Medicine and Nephrology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Ahmed Mohammed Farouk

Prof. of Clinical Pathology, Military Medical Academy, Cairo, Egypt

Mohammad Sobhy Abdulhameed Abdulkhaliq

M.Sc Internal Medicine, Al Galaa Medical Military Complex, Cairo, Egypt, mohammadsobhy9@gmail.com

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Complement Activation and Cytokine Production and Their Relation to Cardiovascular Changes in Hemodialysis Patients

Mohamed Nabil Raafat ^a, Ahmed Alaa Eldin Ahmed Saad ^b, Ahmed Mohammed Farouk ^c,
Mohammad Sobhy Abdulhameed Abdulkhaliq ^{d,*}

^a Department of Internal Medicine and Clinical Immunology, Egypt

^b Department of Internal Medicine and Nephrology, Faculty of Medicine, Al-Azhar University, Egypt

^c Department of Clinical Pathology, Military Medical Academy, Egypt

^d Department of Internal Medicine, Al Galaa Medical Military Complex, Cairo, Egypt

Abstract

Background: End-stage renal disease (ESRD) is a very consequential medical condition that has been identified as a significant concern in the field of public health, impacting a global population exceeding 2.6 million individuals. Despite notable advancements in hemodialysis (HD) treatments over the past few decades, individuals with ESRD continue to have a substantial burden of cardiovascular disease and face a heightened risk of mortality.

Aim: Our study aimed at assessment of complement activation and cytokine production and their relation to cardiovascular changes in HD patients.

Patients and methods: This cross-sectional study was conducted in dialysis units in Al-Hussein University Hospital. Over a period of 6 months (from May 1, 2021 to November 31, 2021), 25 ESRD patients were included in the study as regards the inclusion and exclusion criteria.

Results: The current study showed that there was a significant increase in the right intima-media thickness mean at the end of the study. Left intima-media thickness had a significant correlation with interleukin-6 (IL-6) at the start of the study after 1 h of HD. IL-6 also correlated significantly with the right carotid plaque, left carotid significant stenosis, and left carotid calcification at the end of the study after 1 h of HD. Complement 3d had a significant correlation with ejection fraction% at the start of the study after 1 h of HD.

Conclusion: The current study showed that there was a continuous increase in IL-6 and complement 3d levels in HD patients. This means that complement activation and cytokine production were significantly related to cardiovascular changes in HD patients.

Keywords: Complement 3d, Cardiovascular changes, Hemodialysis, Interleukin-6

1. Introduction

The global incidence of chronic kidney disease (CKD) is steadily rising and is projected to persist in its upward trajectory.¹

There are five distinct stages associated with CKD, with the ultimate stage being end-stage renal disease (ESRD), necessitating renal replacement therapy (RRT) as a critical intervention to sustain life.²

The utilization of RRT is considered a fundamental aspect in the management of individuals diagnosed with ESRD. Hemodialysis (HD) continues to be the prevailing modality for RRT.³

Based on the projections made by predictive models, it is anticipated that the population of individuals with Huntington's disease might potentially increase to approximately four million by the year 2030.⁴

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* Corresponding author at: 7 Abo Elela Street, Zagazig, Sharkia Governorate, Egypt.
E-mail address: mohammasobhy9@gmail.com (M.S.A. Abdulkhaliq).

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HD is an extracorporeal technique used for the purification of blood. Its primary function is the removal of metabolic waste substances, which primarily consist of water and solutes. The procedure employs semipermeable membranes, including diverse separation processes, in order to facilitate blood purification and eliminate uremic toxins.⁵

As the progression of renal disease intensifies, patients experience a multitude of problems that are closely linked to an elevated susceptibility to comorbidities and mortality.²

The life expectancy and quality of life of those undergoing dialysis treatment are comparatively lower than those of the general population. In general, there is a correlation between HD and elevated rates of cardiovascular morbidity and mortality.⁶ The biocompatibility of synthetic or semisynthetic materials in membranes leads to the stimulation of other cells through the generation of a group of mediators.⁷ This series of events will result in the activation of immunoreactive complement.⁸

The activation of the complement system induces the enzymatic cleavage of complement 3 (C3), leading to the generation of two distinct fragments: C3b, a larger fragment, and C3a, an anaphylatoxin. In the course of its degradation, C3b undergoes a sequential breakdown leading to the formation of iC3b, which then transforms into the more structurally stable C3d fragment. This system exhibits a multitude of functions and plays a significant role in the pathophysiology of several disorders.⁹ Numerous investigations have demonstrated a correlation between complement and cardiovascular events.¹⁰ Nevertheless, the association between the activation products of complement and cardiovascular events has not been adequately defined.¹¹

Interleukin-6 (IL-6) is a potent cytokine that can initiate a powerful pro-inflammatory reaction.¹² There is a correlation between an elevated risk of cardiovascular events in both the general population and individuals with CKD.¹³

2. Patients and methods

This study was conducted in dialysis units in Al-Hussein University Hospital. Over a period of 6 months (from May 1, 2021 to November 31, 2021), 25 ESRD patients were included in the study as regards the inclusion and exclusion criteria.

2.1. Inclusion criteria

Represented by patient's age was more than 18 years and HD duration was more than 6 months.

2.2. Exclusion criteria

Represented by those who were 18 years old or younger, those who had not been on HD for at least 6 months, patients previously known to have heart failure, patients who had a history of malignancy, cardiovascular surgeries, or recent infections, and patients who are not regular on HD three sessions/week.

All participants in the study were subjected to the following: informed consent for participation in the study and full history and clinical examination, including demographic data, HD data, and cardiovascular examination.

2.3. Laboratory investigations

Complete blood count, intact parathyroid hormone, serum calcium, serum phosphorus, serum ferritin, and TIBC. Serum electrolytes were measured using a fully automated instrument (AVL-9130), USA. Serum parathyroid hormone was assayed in all patients by the intact parathyroid hormone ELISA Kit. IL-6 and C3d at the start of HD session and after 1 h at the start of the study and at occurrence of a CV event or after 6 months from the start of the study (which was closer).

C3d serum level was measured by Human Complement Fragment 3d ELISA kit (BT LAB Bioassay Technology Laboratory) Cat. No E5115Hu using apDian.V. A.D. WASH ELISA Plate Washer and DIA Sowrce ELISA READER.

IL-6 serum level was measured by human IL-6 ELISA kit (BT LAB Bioassay Technology Laboratory) Cat. No E0090Hu using apDian.V. A.D. WASH ELISA Plate Washer and DIA Sowrce ELISA READER.

2.4. Radiology

2.4.1. Echocardiography

The study employed GEE 95 2D transthoracic echocardiography with a 5 S probe to assess various cardiac parameters, including ejection fraction (EF), left ventricular thickness, segmental wall motion abnormalities, valve lesions, and diastolic dysfunction. These assessments were conducted both at the beginning and end of the study.

2.4.2. Carotid duplex

The utilization of a 11 S (linear) probe was employed both at the initiation and conclusion of the study to assess many factors, including intima-media thickness (IMT), the presence of calcification, plaque, or notable stenosis. The common carotid arteries

were assessed in a supine position with leg support, while the examiner was positioned toward the patient's head, in order to visualize the IMT. The process of neck scanning was improved by the deliberate tilting and rotation of the head away from the side being investigated. Additionally, adjustments were made to accommodate the position of the head and neck throughout the examination, in order to optimize the visualization of the common carotid arteries. Multiple transducer positions were employed in this study to investigate the common carotid arteries along the long-axis (longitudinal) planes. The transverse view of the carotid artery was acquired using either an anterior or lateral/postero-lateral approach, depending on which approach provides the most optimal visualization of the arteries. Far-wall pictures of the common carotid artery were acquired in the longitudinal plane, specifically at a location situated along a 1-cm segment of the artery that is distal to the carotid bulb.

The efficacy of this particular approach for measuring IMT has been demonstrated, establishing it as a straightforward and replicable technique for evaluating IMT of the common carotid artery in typical clinical settings.¹⁴

Participants were examined for IMT (normal values range from 0.4 to 0.7 mm).¹⁵ Values above 1.0 mm were considered as significantly increased¹⁶ plaque and significant stenosis (>60%).¹⁷

2.5. Hemodialysis prescription

All participants had been on HD machines thrice weekly, 4 hs/session using Fresenius 4008B dialysis machines and FX 80 helixone plus dialyzer (high-flux dialyzer with 1.8 m²), blood pump rate 300 ml/h using unfractionated heparin 2000 IU bolus dose followed by infusion of 1000 IU/h.

2.6. Statistical analysis

The data were subjected to analysis using the Statistical Program for Social Science (SPSS), version 20.0. The quantitative data were represented as the mean \pm SD. The qualitative data were represented in terms of frequency and percentage.

3. Results

The results of this study were summarized in the following tables.

Table 1 shows that mean age was 65 \pm 10 years, HD duration ranged between 1 and 12 years. It also shows that 64% of the patients were females and 36% were males.

Table 1. Demographic distribution among the studied patients.

Variables	Studied patients (N = 25)
Age (years)	
Mean \pm SD	65 \pm 10
Range	37–76
HD duration (years)	
Mean \pm SD	4.3 \pm 2.6
Range	1–12
Sex [n (%)]	
Male	9 (36)
Female	16 (64)

HD, hemodialysis.

Table 2 shows that the commonest cause of ESRD was DM (40%) followed by hypertension (28%), then came analgesic nephropathy (8%), and both glomerulonephritis, autosomal-dominant polycystic kidney disease and recurrent urinary tract infection, represented 4% for each. Other causes constituted 12% cumulatively.

Table 3 shows that there is a significant increase in C3d after 1 h of the start of the HD session.

Table 4 shows that there is a significant increase in C3d after 1 h of HD session at the end of the study.

Table 5 shows that there is a significant increase in right IMT mean at the end of the study. However, there is an increase in left IMT mean at the end of

Table 2. Causes of end-stage renal disease distribution among the studied patients.

Variables	Studied patients (N = 25) [n (%)]
Diabetes mellitus	10 (40)
Hypertension	7 (28)
Glomerulonephritis	1 (4)
ADPKD	1 (4)
Recurrent UTI	1 (4)
Analgesic nephropathy	2 (8)
Other causes	3 (12)

Table 3. Interleukin-6 and complement 3d levels among the studied patients at the start of the study.

Variable	Studied patients (N = 25)		P
	Before session	After 1 h	
IL-6 (μ g/ml)	2.3 \pm 0.856	2.53 \pm 1.46	0.183
C3d (μ g/ml)	19.49 \pm 9.18	22.81 \pm 11.23	<0.001

Table 4. Interleukin-6 and complement 3d levels among the studied patients at the end of the study.

Variables	Studied patients (N = 20)		P
	Before session	After 1 h	
IL-6 (μ g/ml)	2.62 \pm 1.57	2.9 \pm 2.15	0.077
C3d (μ g/ml)	23.9 \pm 15.01	28.31 \pm 14.72	0.001

Table 5. Intima-media thickness among the studied patients at the start and the end of the study.

Variables	Studied patients (N = 20)		P
	Start of study	End of study	
Right IMT (mm)	0.691 ± 0.110	0.701 ± 0.117	0.036
Left IMT (mm)	0.734 ± 0.157	0.743 ± 0.155	0.068

the study but without a statistically significant difference.

Table 6 shows that 56% of the patients showed no CV events. One patient reported with cerebrovascular stroke and two patients underwent PCI. One patient showed duplex changes but without manifestation. Meanwhile, five (20%) patients died from noncardiovascular causes.

Table 7 shows that only left IMT had a significant correlation with IL-6 at the start of the study after 1 h of HD.

Table 8 shows that IL-6 significantly correlated with right carotid plaque, left carotid significant stenosis, and left carotid calcification at the end of the study after 1 h of HD.

4. Discussion

Comparable with the current study, Major *et al.*¹⁸ showed that the patients with ESRD were predominantly females 57.5% with mean age of 75.9 years.

Table 6. Outcome distribution among the studied patients.

Variables	Studied patients (N = 25) [n (%)]
No CV events	14 (56)
Cerebrovascular stroke	1 (4)
MI	2 (8)
Duplex changes	1 (4)
Positive duplex from the start	2 (8)
Mortality	5 (20)

Table 7. Correlation between interleukin-6 after 1 h of hemodialysis session, at the start of the study, and duplex findings.

Items	Variable	n (%)	P value
Right IMT	Mean ± SD	6.97 ± 0.98	0.223 ^P
Right carotid plaque	Present	8 (32)	0.737 ^t
	Absent	17 (68)	
Right carotid significant stenosis	Present	2 (8)	0.706 ^t
	Absent	23 (92)	
Right carotid calcification	Present	10 (40)	0.518 ^t
	Absent	15 (60)	
Left IMT	Mean ± SD	7.04 ± 1.03	0.090 ^P
Left carotid plaque	Present	10 (40)	0.398 ^t
	Absent	15 (60)	
Left carotid significant stenosis	Present	4 (16)	0.469 ^t
	Absent	21 (84)	
Left carotid calcification	Present	7 (28)	0.179 ^t
	Absent	18 (72)	

IMT, intima-media thickness.

Table 8. Correlation between interleukin-6 after 1 h of hemodialysis session, at the end of the study, and duplex findings.

Items	Variable	n (%)	P value
Right IMT	Mean ± SD	6.90 ± 0.97	0.397 ^P
Right carotid plaque	Present	6 (30)	0.019 ^{t*}
	Absent	14 (70)	
Right carotid significant stenosis	Present	1 (5)	0.658 ^t
	Absent	19 (95)	
Right carotid calcification	Present	6 (30)	0.141 ^t
	Absent	14 (70)	
Left IMT	Mean ± SD	7.03 ± 1.06	0.653 ^P
Left carotid plaque	Present	6 (30)	0.141 ^t
	Absent	14 (70)	
Left carotid significant stenosis	Present	3 (15)	0.043 ^{t*}
	Absent	17 (85)	
Left carotid calcification	Present	6 (30)	0.044 ^{t*}
	Absent	19 (70)	

IMT, intima-media thickness.

The current study also showed that the commonest cause of ESRD was DM (40%) followed by hypertension (28%), then came analgesic nephropathy (8%), and both glomerulonephritis, autosomal-dominant polycystic kidney disease and recurrent urinary tract infection, represented 4% for each. Other causes constituted 12% cumulatively.

In concordance with the current study, Fukushi *et al.*¹⁹ showed that the most common etiology of ESRD was diabetic kidney disease (40%).

At the start of the study, it was revealed that there was a significant decrease in potassium, creatinine, and urea after the HD session. Also, at the end of the study, there was a significant decrease in potassium, creatinine, and urea after HD session.

In agreement with the current study, Vaziri *et al.*²⁰ showed that HD resulted in significant reduction in serum urea, creatinine, and potassium concentrations. The same results were reported by Astan *et al.*²¹

In relation to the IL-6 and C3d levels seen in the participants under investigation at the commencement and conclusion of the study, it was discovered that there was a notable elevation in C3d levels following 1 h from the initiation of the HD session. However, there was no substantial rise in IL-6 levels after 1 h from the commencement of the HD session.

This was supported by Poppelaars *et al.*²² The assessment of complement activation was conducted by evaluating the C3d/C3-ratio in a cohort of 55 patients during a single HD session at the initiation of the follow-up period. The findings demonstrated a significant increase in the C3d/C3-ratio after 30 min from the commencement of the HD session. This increase was observed in both patients with and without cardiovascular events, although the

magnitude of the increase was greater in patients with cardiovascular events.

Regarding the carotid duplex ultrasound findings among the studied patients, the study findings indicate that there was no statistically significant alteration in the clinical characteristics observed between the study's commencement and conclusion.

This was supported by Muzasti *et al.*²³ The study findings indicated that the average length of HD was 81.28 ± 67.40 months. Furthermore, the analysis revealed no statistically significant association between the duration of HD and the presence of carotid artery calcification. The occurrence of vascular calcification is not limited to a specific time period but can commence at an early age.²⁴

The present investigation demonstrated a notable elevation in the mean right IMT upon completion of the study. Nevertheless, it is worth noting that there was a rise in the mean left IMT toward the conclusion of the trial; nevertheless, this increase did not reach statistical significance.

Also, our results were further supported by Arda-hanli *et al.*²⁵ The individuals who disclosed the mean carotid intima-media thickness (CIMT) measurements were 0.86 ± 0.16 mm in the group of patients with ESRD on HD, and 0.61 ± 0.11 mm in the control group. The average CIMT was found to be considerably greater in the patient group ($P < 0.001$). The study's findings indicated that CIMT had a higher degree of prominence as an indicator of atherosclerotic progression in patients with heart disease.

The echocardiography findings of the patients under examination at the beginning and conclusion of the trial did not exhibit any statistically significant alterations.

In this study, 16% of the patients presented with hypertrophic left ventricular at the start of the study and then became 10% at the end of the study.

There is also a decrease in diastolic dysfunction grade at the end of the study. About 36% of the patients presented with segmental wall motion abnormalities at the start of the study and then became 40% at the end of the study. About 8% of the patients presented with dilated right side at the start of the study than none who showed dilated right side at the end of the study.

Regarding valvular morphology among the studied patients, it was revealed that there is a general decrease in valvular disease percentage at the end of the study.

Regarding outcome distribution among the studied patients, the current study showed that 56% of the patients showed no CV events and 30% showed CV events. One patient reported with cerebrovascular stroke and two patients underwent

PCI. One patient showed duplex changes but without manifestation. Meanwhile, five (20%) patients died from noncardiovascular causes.

Similar to the current study, Poppelaars *et al.*²² showed that there were 30.1% of the studied HD patients who have CV events.

Our results were supported by Muzasti *et al.*²³ the individual(s) responsible for demonstrating that an elevated concentration of IL-6 is associated with an increased likelihood of carotid artery calcification in patients with stage-5 CKD on dialysis.

A cross-sectional study by Kato *et al.*²⁶ the study observed an elevated concentration of IL-6 in individuals undergoing HD who had atherosclerosis, in contrast to the control group consisting of healthy individuals.

In relation to the association between C3d levels following a 1 h HD session, both at the beginning and conclusion of the study, and the findings from carotid duplex examinations, it was seen that there was no statistically significant correlation between C3d levels and any of the carotid duplex parameters examined at the start and end of the study following a 1 h HD session.

In agreement with the current study, Barberato *et al.*²⁷ found no association between IL-6 and echocardiographic indices in patients on HD.

Regarding the correlation between C3d after 1 h of HD session and echocardiography findings, at the start of the study, it was revealed that C3d had a significant correlation with EF% at the start of the study after 1 h of HD. However, at the end of the study, C3d had no significant correlation with any of the studied echocardiography items at the end of the study after 1 h of HD.

Our results were supported by Poppelaars *et al.*²² The individual who disclosed the finding that HD patients who experienced cardiovascular events during the follow-up period exhibited a greater intradialytic C3d/C3-ratio was not specified. Furthermore, it was observed that the IL-6/IL-10 ratios remained elevated in the group of HD patients who experienced a cardiovascular event during the follow-up period. This finding indicates a statistically significant difference between the two groups at this particular time point ($P < 0.05$). In general, heightened concentrations of pro-inflammatory and pro-thrombotic agents appear to precede the occurrence of cardiovascular events in individuals using HD.

4.1. Conclusion

The present investigation revealed a persistent elevation in IL-6 and C3d concentrations among

individuals undergoing HD. This means that complement activation and cytokine production were significantly related to cardiovascular changes in HD patients. Elevated C3d and IL-6 were identified as risk factors of cardiovascular events in HD patients.

4.2. Recommendations

We recommend the use of IL-6 and C3d in the follow-up as predictors of cardiovascular events in HD patients. Further studies with larger number of patients and extended study duration are required. Further studies should also have a special concern regarding the echocardiography and carotid duplex findings related to the elevated levels of serum C3d.

Conflicts of interest

There are no conflicts of interest.

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