Journal of International Medical and Biological Sciences
ISSN: 2617-8885
International Peer Reviewed
JIMBS

Original Article

Inflammation , Atherosclerosis and Malnutrition Syndrome among Iraqi Patients on Hemodialysis: A Prospective Clinical Study

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Received: January, 2023, Accepted and Published online: April, 2023,

Abstract:

Background: *In dialysis patients, the main cause of death is cardiovascular diseases, however, several studies documented a role for malnutrition and inflammation in the occurrence of atherosclerosis, which in turn leads to increased mortality rates among dialysis patients.*

Objective: *To estimate the prevalence of inflammation, malnutrition, and atherosclerosis among Iraqi patients with renal failure on maintenance hemodialysis*

Materials and methods: *This was a prospective clinical study conducted during a period of 18 months in Karbala. All patients were followed up and various information related to them (age, gender, medical condition, ...) were recorded. In addition, Doppler sonar , echocardiography and other necessary investigations were performed accordingly. Statistical analysis was done using the statistical package for social sciences (SPSS 25), All statistical procedures and correlation analysis were performed at a level of signifciance of 0.05.*

Results: *We found atherosclerosis in 54 patients (62.8%), Malnutrition in 46 (53.5%) and inflammation in 39 patients (45.3%). C-reactive protein (CRP) was elevated in 45 cases (52.3%). Low level of albumin reported in 61.6% of cases. A significant negative (inverse) correlation was found between CRP and albumin, while a significant positive correlation was found between CRP and atherosclerosis.*

Conclusions: *A high percentage of hemodialysis patients have malnutrition, inflammation, and atherosclerosis. A significant inter-correlation between these three conditions in ESRD patients. High levels of CRP was associated with hypoalbuminemia, which reflect the association between inflammation and malnutrition*

Keywords: *Inflammation , Atherosclerosis and Malnutrition, syndrome, MIA, Hemodialysis, ESRD , Iraqi Patients.*

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***Citation**: Sabri N.M.M, Inflammation , Atherosclerosis and Malnutrition syndrome among Iraqi Patients on Hemodialysis A Prospective Clinical Study. JIMBS 2023; 9 (1):71-85*

1. INTRODUCTION

As a result of a mostly progressive impairment of kidney function, multiple disorders occur in various organ systems, which ultimately make the initiation of renal replacement therapy mandatory. The term "renal replacement therapy" includes hemodialysis, peritoneal dialysis and kidney transplantation (1). Many different underlying diseases can lead to chronic kidney failure. The most common causes are secondary nephropathies due to underlying diseases, such as arterial hypertension and diabetes mellitus (2). However, interstitial and glomerular nephritis as well as systemic diseases, such as lupus erythematosus or vasculitis, can also lead to a long-term loss of kidney function (3). However, considerable proportion of patients with chronic renal insufficiency, the genesis of their disease remains unknown (4).

As a result of the manifold tasks of the kidney, a restriction of kidney function is accompanied by numerous disorders in various organ systems (5). Due to a reduced synthesis of erythropoietin in the proximal tubule cells and the interstitial fibroblasts, a mostly normochromic, normocytic anemia, the so-called renal anemia, occurs (6). The hydroxylation of calcidiol to calcitriol, the so-called active vitamin D_3, also takes place only to a limited extent this results in a reduced absorption of calcium and phosphate from the intestine, a reduced mineralization of the bones, as well as a disorder of tubular calcium and phosphate reabsorption (7),.

In addition, reduced filtration leads to an impairment of the water and electrolyte balance, hyperhydration with edema and congestion symptoms, hyperkalemia can occur. Another consequence of chronic renal insufficiency is decreased acid excretion capacity (8). The resulting metabolic acidosis can lead to gastrointestinal symptoms such as nausea and loss of appetite as well as protein catabolism . Finally, the accumulation of urinary substances also leads to their transfer into the human blood. This so-called uremia is assessed by means of urea concentration in plasma. The clinical presentation of uremia ranges from central nervous system symptoms such as somnolence, loss of appetite and nausea to pruritus or pleurisy. It is often associated with malnutrition and oxidative stress (9–11).

However, one of the major problems with chronic kidney failure is accelerated atherosclerosis, which leads to a huge increase in cardiovascular risk. It has been suggested that CKD patients have higher risk of premature death mainly due to CVD and the association between CKD on HD and accelerated atherosclerosis has been widely documented more 40

years ago. Recently, it has been observed that of atherosclerosis can occurs at early stages of CKD (12).

There are two main pathogenesis mechanisms underlying atherosclerosis in CKD patients ; on one hand, the reduced GFR can leads to an accumulation of phosphate; in CKD patients, hyperphosphatemia exacerbates atherosclerosis exacerbated by hyperphosphatemia through a minnosidases mediated complex-type conversion of SCAP N-glycans (13). On the other hand, atherosclerosis is caused by atherosclerotic lipid deposits in the blood, which are probably caused by inflammatory and macrophage activity (14,15). Chronic kidney disease and renal insufficiency, especially dialysis patients, often have increased inflammatory markers. On the basis of this pathogenetic relationship, they can thus be seen as a risk factor for increased cardiovascular mortality. As mentioned earlier, malnutrition is also a common problem in dialysis patients, which is also associated with increased inflammatory activity and mortality (16,17).

Malnutrition is a very common problem in CKD patients with a prevalence ranges between 20-50%. The prevalence rate varies widely due to differences in the diagnostic tools , and is associated with increased mortality and morbidity in this patient population (18). Malnutrition usually develops before entering a stage of renal insufficiency requiring dialysis, with albumin, transferrin and cholesterol as markers of nutritional status (19).

Inflammation is known to be associated with poor outcome in chronic renal failure. The causes underlying this high prevalence of inflammatory markers in CKD patients is not yet fully understood. Some pathomechanisms are discussed as triggers of the inflammatory response such as a reduction in renal function may be accompanied by reduced renal clearance of inflammatory factors. These could then directly or indirectly promote the development of an inflammatory response. Hypervolemia induced by renal insufficiency alters the permeability of the gastrointestinal tract and thus leads to an accumulation of lipopolysaccharides and bacteria, which in turn favors the release of proinflammatory cytokines (20–23). Another hypothesis is that oxidative stress, whether due to low levels of antioxidants or increased production of free radicals, leads to increased cytokine release.

Any comorbidities, such as diabetes mellitus, can also contribute to the development of inflammatory conditions. Since dialysis patients are more susceptible to infections due to uremia, comorbidities and old age, an infection-related inflammatory reaction is also a possible pathomechanism (20–23).

However, the dialysis procedure itself can also be considered as an inflammatory factor (24). Inflammation is thought to play a major role in the development of atherosclerosis . For example, CRP is not only seen as a sign of inflammatory activity, but also as an indicator of mortality and cardiovascular mortality in particular (25).

In order to take into account the close relationship between malnutrition, inflammation and atherosclerosis and their significant involvement in the mortality of dialysis patients, the term malnutrition-Inflammation complex syndrome (MICS) was introduced (20). In order to emphasize the association with arteriosclerotic cardiovascular diseases, the term malnutrition, inflammation, arteriosclerosis syndrome (MIA syndrome) was also utilized (26).

2. PATIENTS AND METHODS

This was a prospective study conducted during a period of 18 months in Karbala city, included 86 patients on maintenance hemodialysis.

Inclusion criteria:

1. Iraqi patients on regular maintenance hemodialysis
2. Adult of a minimum age of 20 years
3. Both males and females were included

Exclusion criteria:

1. Patients with malignant diseases
2. Existing infection with hepatitis B or C
3. Patient who had Liver diseases
4. Patient with Autoimmune disease
5. Stop the dialysis or missed to follow up

Data collection:

In addition to the patient's demographic characteristics; age and gender, the following data were taken from which were entered into a computerized database in the manner described in each case. Microsoft Excel 2020 used for this purpose. Full history taken and thorough clinical examination were assured . History and clinical data were collected and include the following:

Comorbidities at the time of first dialysis such as- Diabetes mellitus, hypertension, CHD, or other heart disease, vascular disease, COPD, date of first dialysis, dialysis modality at the time of first dialysis , body weight, body mass index (BMI) at the time of first dialysis, center

of primary dialysis , If a case died , date of death, cause of death (died cases were excluded from the study).

In addition, the following laboratory values were extracted from the patients' medical files at the time of the first dialysis and entered into the existing database . Laboratory parameters included C-reactive protein (CRP) (mg/dL), Albumin (g/dL), Hemoglobin (g/dL), Calcium (mmol/L), Phosphate (mmol/L) and PTH (pg/mL). In addition to the virology studies

Statistical analysis:

The created database was imported into IBM SPSS Statistics 26 and evaluated anonymously. Statistical significance was assumed at a p-value of ≤ 0.05. Differences in frequency that occurred in a group comparison were evaluated using the Chi square test. The mean value comparison between groups was carried out using a t-test and ANOVA accordingly.

3. RESULTS

The study included 86 patients of both genders; 52 males and 34 females contributed for 60.5% and 39.5%, respectively, with a male to female ratio of almost 1.5 to one (**Figure 1**). The mean age of the patients was 54.2 ± 12.6 (range: 35 – 69) years, moreover, 67.4% of the patients were older than 50 years. Family history of CKD reported in 14%, overweight and obesity in 73.3%, and smokers were 29.1% of the studied group, (**Table 1**). The frequency distribution of comorbidities among the 86 HD patients is shown in (**Table 2**) where hypertension was the more frequent underlying comorbidity which account for 69/86 (80.2%), followed by dyslipidemia (62.8%), Vascular disease (PAD, CVC), CHD, diabetes mellitus, heart failure and COPD which are found in 55.8%, 45.3%, 39.5%, 34.9% and 15.1%, respectively. However, majority of the patients had more than one comorbidity.

Regarding the MIA syndrome components we found atherosclerosis in 54 patients (62.8%), Malnutrition in 46 (53.5%) and inflammation in 39 patients (45.3%), (**Figure 2**).

The mean values, standard errors and 95% confidence intervals of the Laboratory parameters of the studied group are summarized in (**Table 3**). On the other hand, the levels of these parameters are shown in (**Table 4**), where C-reactive protein (CRP) was elevated in 45 cases (52.3%), PTH was elevated in 28 cases (32.6%) while low levels reported in 61 cases (70.9%). Hyperglycemia reported in 61.6% while low blood glucose found in only 5 cases (5.8%). Elevated PO4 found in (55.8%), low s. calcium in (59.3%). Hemoglobin (HGB) < 10

g/dL observed in 75.6% while 24.4% of cases had HGB of 10-12 g/dL. Low level of albumin reported in 61.6% of cases.

Further analysis was performed using bivariate correlation analysis; the Pearson's and Spearman's rho tests, to assess the correlation between different parameters and variables. Results of this analysis are demonstrated and highlighted in (**Table 5**). According to this analysis, the main significant finding correlation was found as followed:

A significant negative (inverse) correlation was found between CRP and albumin, while a significant positive correlation was found between CRP and atherosclerosis. Other significant correlations were found between atherosclerosis was inversely and significantly correlated with albumin and each of age, smoking, hypertension, diabetes mellitus (DM), dyslipidemia and longer duration on HD, in all these correlations, P. value <0.05. No other significant pairwise correlation was found.

Table 1. Demographic characteristics of the studied group (N=86)

Variable		No.	%
Age (year)	≤ 40	10	11.6
	41 - 50	18	20.9
	51 - 60	27	31.4
	> 60	31	36.0
	Mean age (SD)	54.2 (12.6)	-
	Range	35 - 69	-
Gender	Male	52	60.5
	Female	34	39.5
	Ratio	1.5: 1.0	-
Family history of CKD	Yes	12	14.0
	No	74	86.0
BMI	Normal	23	26.7
	Overweight	41	47.7
	Obese	22	25.6
Smoking	Yes	25	29.1
	No	61	70.9

BMI: body mass index, SD: standard deviation

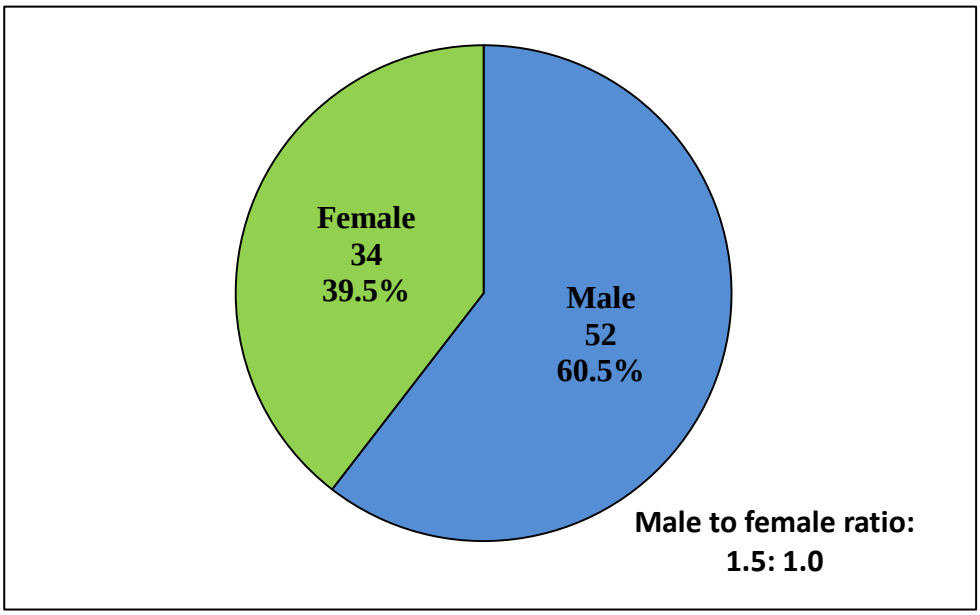

Figure 1. Distribution of the studied group according to gender with Male to Female ratio

Table 2. Frequency distribution of comorbidities among 86 HD patients

Comorbidities	No.	%
Hypertension	69	80.2
Dyslipidemia	54	62.8
Vascular disease (PAD, CVC)	48	55.8
CHD	39	45.3
Diabetes mellitus	34	39.5
Heart failure	30	34.9
COPD	13	15.1

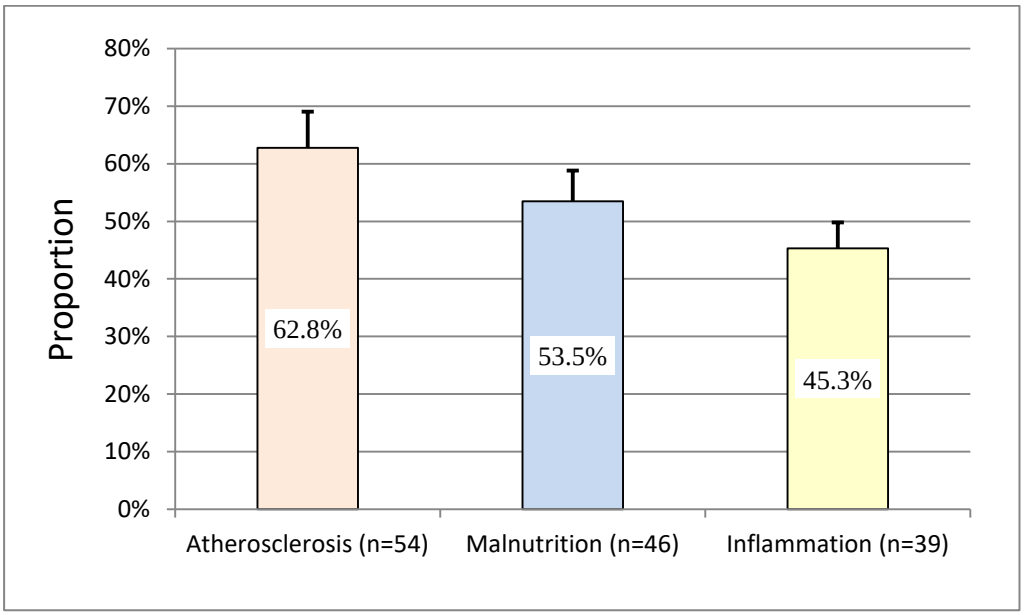

Figure 2. Proportional distribution of the MIA components among the studied group

Table 3. Laboratory parameters of the studied group (N=86)

Parameter	Mean	SE	95% CI	
			Lower limit	Upper limit
Blood urea (mg/dl)	133.2	2.0	129.3	137.1
S. creatinine (mg/dl)	6.11	0.13	5.9	6.4
CRP (mg/dl)	4.08	0.22	3.6	4.5
PTH (ng/ml)	346.28	23.17	300.9	391.7
Blood glucose (mg/dl)	124.31	1.34	121.7	126.9
PO4 (mg/dl)	4.73	0.12	4.5	5.0
S. calcium (mg/dl)	7.72	0.11	7.5	7.9
Hemoglobin (g/dl)	10.44	0.15	10.1	10.7
S. Albumin (g/L)	38.21	0.76	36.7	39.7

SE: standard error of mean, 95% CI: 95% confidence interval of mean

Table 4. Status of levels of Laboratory parameters of the studied group (N=86)

Parameter		No.	%
CRP	Normal	41	47.7
	Elevated	45	52.3
PTH	Normal	25	29.1
	Elevated	28	32.6
	Low	61	70.9
Blood glucose	Normal	28	32.6
	Elevated	53	61.6
	Low	5	5.8
PO4	Normal	38	44.2
	Elevated	48	55.8
S. calcium	Normal	35	40.7
	Low	51	59.3
Hemoglobin	< 10	65	75.6
	10 - 12	21	24.4
S. Albumin	Normal	33	38.4
	Low	53	61.6

Blood urea and S. creatinine were elevated in all patients

Table 5. Results of multiple pairwise correlation analysis of the studied parameters and variables

Variable/Parameter	*Statistics*	CRP	Albumin	Atherosclerosis
Albumin	*R*	-0.793	-	
	P. value	0.001	-	
Atherosclerosis	*R*	0.622	0.102	-
	P. value	0.001	0.397	-
Age	*R*	0.334	0.108	0.526
	P. value	0.012	0.192	0.002
Gender	*R*	0.128	0.060	0.089
	P. value	0.193	0.202	0.688
Smoking	*R*	0.028	0.084	0.502
	P. value	0.893	0.194	0.004
Hypertension	*R*	0.104	0.036	0.765
	P. value	0.496	0.204	0.001
DM	*R*	0.095	0.027	0.560
	P. value	0.895	0.197	0.007
Dyslipidemia	*R*	0.023	-0.128	0.405
	P. value	0.632	0.207	*0.030*
Duration on HD	*R*	0.309	0.112	0.524
	P. value	0.021	0.394	0.005

4. DISCUSSION

In dialysis patients, the occurrence of a combination of malnutrition, inflammation and atherosclerosis (MIA syndrome) is associated with increased general and also cardiovascular mortality which is the most common cause of death in dialysis patients. The second most common cause of death is infection (18,20,26). In these patients, higher mortality rates due to cardiovascular complications suggest an accelerated atherogenesis with its adverse consequences like peripheral, cerebral and cardiac ischemic disorders. Previous studies and literatures reported that dialysis patients more liable to have carotid and coronary atherosclerosis (12,25,26). However higher incidence of increased intima media thickness of the carotid artery has shown in hemodialysis patients and the fact that CKD considered as a significant predictor of increased intima media thickness and atherosclerosis (27,28). From other point of view, previous studies have shown that malnutrition is frequently incident in CKD patients and in an average up to 50% of hemodialysis patients have some sort of malnutrition (18), which reflected by a low serum albumin level which is considered as a marker of malnutrition (19). Additionally, different metabolic disorders, mineral disturbances and atherothrombogenic disorders occur in hemodialysis patients due to different pathogenic mechanisms, inflammation and atherosclerosis (20,26,29). Therefore, we aimed in this study to assess the prevalence of malnutrition, atherosclerosis and inflammation among group of Iraqi patients on hemodialysis. Hence a total of 86 ESRD patients of both genders who met the selection criteria were enrolled in this study. Age distribution of the studied group revealed that almost two-thirds of the patients were older than 50 years with a mean age of 54.2 years, and predominance of males than females in a ratio of 1.5 to one . This finding consistent with the epidemiological characteristics of ESRD and hemodialysis patients. Furthermore, our findings regarding the demographic characteristics, family history of CKD, body mass index and smoking history of the studied group all are consistent with previous studies concerned with hemodialysis patients in Iraq (30), moreover, Lee et al. documented that CKD increased with older age , the prevalence was high in males and smokers (31).

In our cohort, frequency distribution of comorbidities among the 86 HD patients showed that hypertension, dyslipidemia vascular disease, CHD, DM and H eart failure are commonly found in these patients in addition to COPD, these findings were not unexpected due to the nature of the ESRD and its complications in addition, some of these comorbidities could be

predisposing factors that contribute to the development of CKD that needed hemodialysis, similarly, previous studies documented that these comorbidities are common in such population of ESRD patients in Arab countries (32), from other point of view, patients with at least three comorbidities, initiated dialysis earlier than those with no comorbidities. The risk of multiple comorbidity is high in older age patients, smokers and those with proteinuria , from other point of view, multicomorbidity increases the risk of poor outcome in hemodialysis patients (31)

In our study we found that atherosclerosis, malnutrition and inflammation were frequent among the studied group in a rate of 62.8%, 53.5% and 45.3%, respectively. These findings close to that reported in previous local and international studies. In a previous Iraqi study conducted by Allawi A. in 2016 (30), prevalence of atherosclerosis, malnutrition and inflammation was 65.3%, 58.4% and 43.6%, respectively, which close to our findings. Other studies also showed that atherosclerosis, malnutrition and inflammation are common in CKD patients; Fouque et al. from France showed that 18-75% of patients on maintenance hemodialysis had wasting and malnutrition (33), Kalantar-Zadeh (34) documented that inflammation and protein-energy malnutrition are two conditions that quite common and co-occurring in CKD patients and have been identified as the primary causes of short-term mortality in these patients. One of the primary causes of atherosclerotic heart disease in the CKD population appears to be the "Malnutrition, Inflammation and Cachexia Syndrome" (MICS) (20,34). A long-lasting cachexia is brought on by MICS when there is low homocysteine and cholesterol levels, thus, a reversed epidemiology of cardiovascular risk factors in dialysis patients results in an increased association between obesity, hypercholesterolemia, and hyperhomocysteinemia with increased survival(35).

Wang et al. (36) reported that microinflammatory status in HD patients that underlying the CKD is aggravated by abnormal immune system. The contact of blood with dialysis membrane, urotoxin accumulation, translocation of endotoxins and accumulation of inflammatory factors all trigger the complement system activation. Additionally, the inflammation itself act as a catalyst for and contribute to the development of cardiac insufficiency and complications. Despite the fact that many factors associated with nutritional state of CKD patients, inflammation is the most important and significant factor. Low albumin level which is commonly found in CKD patients has shown to be associated with inflammation and also considered as a poor nutritional marker in CRF patients (30,37)

We documented a strong negative correlation between CRP and serum albumin.

Other investigators showed that CRP was a strong predictor of serum albumin level in HD patients and that the higher CRP to albumin ratio associated with higher six-months mortality in HD patients (38).

Our study documented a strong correlation between elevated CRP and atherosclerosis which supported by the findings of other studies (38–40); where CRP has shown to be elevated in 30-50% of dialysis patients and can be a predictor of cardiovascular morbidity and mortality. Also it has shown that increased CRP levels reflect the underlying atherosclerosis (40). Furthermore, other studies documented an association between CRP , albumin and CVD in HD patients (41). We proved in this study an association between the three components of MIA in HD patients, and high rates of traditional risk factors included hypertension, DM, dyslipidemia, obesity, smoking in CKD patients. Almost similar findings reported in previous studies from Iraq (30) and other countries (42–44).

5. CONCLUSION

Malnutrition, atherosclerosis and inflammation are common in ESRD patients on maintenance hemodialysis. There was a significant inter-correlation between these three conditions in ESRD patients. High levels of CRP was associated with hypoalbuminemia, which reflect the association between inflammation and malnutrition. We recommend conducting further studies with larger sample included multiple centers for further assessment.

Ethical Issues: All ethical issues were approved by the authors from the Iraqi Ministry of Health. Verbal and signed informed consents were obtained from all patients who included in the study during their first visit.

Conflict of interest: None

Source of funding: Authors declared no funding agency, or organization

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