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Malnutrition-Inflammation complex syndrome in Libyan patients with end-Stage renal disease at Hun-Aljufrah

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Highlights

- **Diabetes and Hypertension are the leading cause of ESRD.**
- **Serum Albumin, BMI and hs-CRP are sensitive markers for MIA Syndrome**
- **Serum Albumin and hs-CRP are negatively correlated in ESRD patients**

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CKD Chronic Kidney Disease, **HD** hemodialysis, **PEM** protein-energy malnutrition, **BMI** Body mass index, **MIA Syndrome** Malnutrition-Inflammation-atherosclerosis Syndrome, **ESRD** End-Stage Renal Disease

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ABSTRACT

Malnutrition and inflammation complex syndrome in ESRD Patients on maintenance Hemodialysis therapy remains the most common cause of morbidity and mortality characterized by alteration in the structural and functional ability of plasma proteins. The aim of this study was to assess the serum level of albumin, BMI and hs-CRP as a marker of Malnutrition-Inflammation Complex Syndrome. This is a case-control study conducted at Alafia Hospital Hun-Aljufrah from December 2014 to December 2015. Libyan patients with ESRD who routinely attend to dialysis center at the above-mentioned hospital during the period of the study were randomly recruited for this study. The study included one hundred ESRD and one hundred age and sex-matched healthy controls. The patients' information such as age, sex, height, weight, and clinical history were recorded. Blood samples (6 ml) were collected from patients in plain and EDTA containers from which EDTA and Serum samples were separated. The results of our study showed that there were significant decrease in the mean serum level of albumin (3.12±0.39) (p. value=0.000) and BMI (20.3±5.5) (p. value=0.000) as well as significant increase in the mean serum level of serum C-reactive protein (20.13±5.704) (p. value=0.000) in case group when compared to the control group. The DOT Blot Correlation test showed that there was a significant negative correlation between hs-CRP with albumin (r= –0.812, p=0.02). In conclusion, the significant decreased in the mean level of serum albumin and BMI, as well as the significant increase in the mean level of serum C-reactive protein among hemodialysis ESRD patients, might place them at risk of developing Malnutrition-Inflammation Complex Syndrome in the future. The significant negative correlation between serum albumin with hs-CRP support the facts systemic inflammation is the main cause of malnutrition and cardiovascular disease in ESRD patient.

1. Introduction

Patients undergoing hemodialysis have a high prevalence of protein-energy malnutrition and inflammation. Those conditions often occur together in ESRD patients on maintenance hemodialysis therapy, they have been referred to the malnutrition-inflammation-atherosclerosis syndrome (MIA syndrome) to confirm their important association with atherosclerotic cardiovascular disease. Chronic kidney disease is an effective disease command by multiple factors that affect its progression and prognosis. The prevalence of dialysis-treated ESRD was 624 per million populations.

2. Protein Energy Malnutrition (PEM)

Known as protein-calorie malnutrition it refers to a form of malnutrition where there is an inadequate supply of protein that is not enough to meet the body's metabolic demands due to either an inadequate dietary intake of protein or increased demands due to disease, or increased protein losses.

2.1 Epidemiology

Recent studies report that 20–50% of ESRD Patients on maintenance haemodialysis therapy suffer from PEM. In most of the hemodialysis patients, malnutrition extends from mild to moderate and only 10% of the haemodialysis ESRD have severe Protein Energy Malnutrition (PEM). In spite of the high prevalence of malnutrition, it was rarely listed as a cause of death in CKD patients on maintenance haemodialysis therapy because malnourished patients die from cardiovascular disease. The strong relationship between malnutrition, inflammation, and arteriosclerosis (MIA-syndrome) in CKD patients on maintenance hemodialysis therapy, suggesting that systemic inflammation participates in the acceleration of the incident of atherosclerosis and malnutrition on hemodialysis ESRD patients (Stenvinkel *et al.*, 2005).

2.2 Malnutrition in patients with MIA Syndrome

It has been recently reported that a systemic inflammatory response may take part in developing hypoalbuminemia in CKD patients on maintenance hemodialysis (Lim VS, 2001). The systemic inflammatory process stimulated by many factors as a uremic state, dialysis membranes, dialysis solution, and infection, causing down-regulation of the cellular metabolism and reduction of the protein synthesis causing acceleration in the negative balance and protein degradation (Stenvinkel *et al.*, 2000).

Malnutrition in CKD patients on maintenance hemodialysis caused by uremic syndrome, comorbid conditions, and inflammation (Chung *et al.*, 2000). Malnutrition is often present in early

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stages of chronic renal failure which characterised by a loss of skeletal muscle mass but a preservation of fat mass (O' Sullivan *et al.*, 2002), This loss result from uraemia, or from inflammation, metabolic acidosis and nutritional deficiency and supposedly hyperleptinemia (Bárány *et al.*, 1997). During the evaluation of chronic renal failure, malnutrition can appear when glomerular filtration assessed by creatinine clearance becomes lower than 40 ml/min/1.73m and there was different mechanism can explain this state of malnutrition as reduction in protein and caloric intakes, deterioration of the renal function, disorders in metabolism of the main nutrients and increased protein catabolism due to acidosis, infections, and inflammations (Aparico *et al.*, 1997). The various aspects of the pathophysiology of malnutrition in HD patients are (schematically presented in Fig. 1 (Alfonso, 2001).

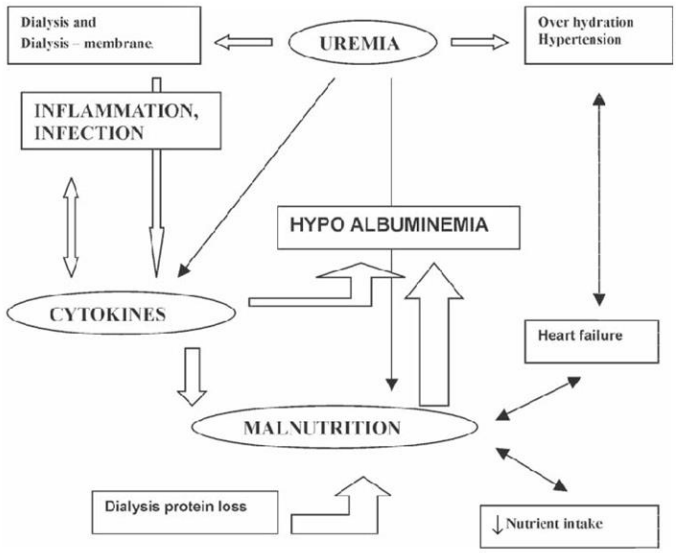

Fig. 1. Pathophysiology of malnutrition in patients with MIA syndrome (Alfonso, 2001).

2.3 Laboratory parameters

Laboratory techniques depend on the determination of the plasma protein levels mainly the negative acute phase reactant. The evaluation of nutritional status depends on an assessment of biochemical laboratory parameters combined with biophysical markers; both will help to find the onset of nutritional disorders and rapid assessment of ongoing treatments.

2.3.1 Serum albumin (half-life 20 days)

Serum albumin levels have been used to assess malnutrition in an individual with and without chronic renal failure (CRF). Serum albumin level is a long-term blood marker of nutritional status (half-life 3 weeks), Malnutrition and hypoalbuminemia were common in hemodialysis CKD patients due to a group of pathological conditions such as hypertension, cardiovascular disease, inflammation, infection, low nutrient intake, protein loss through dialysis and systemic inflammatory response (Kaysen *et al.*, 1995). Albumin has been considered as a negative acute-phase protein because it is level fall actually with inflammation, thus it can be used as an indicator of chronic inflammation.

Hypoalbuminemia in CKD patients on maintenance hemodialysis therapy patients can be a consequence of a combination of malnutrition and inflammatory reactions (Lowrie *et al.*, 1995). Serum albumin and pre-albumin levels were negatively correlated with mortality in patients on maintenance dialysis (Bossola *et al.*, 2005). Many studies have classified the diverse levels of malnutrition by using serum albumin the shows that serum albumin levels of 3.5g/dL or greater are considered normal, serum albumin levels of 2.7g/dL indicate moderate malnutrition, and levels serum albumin level of less than 2.1g/dl indicate severely depleted levels (Storker *et al.*, 1982).

2.3.2 C-reactive protein (CRP)

Is a positive acute-phase reactant whose levels are elevated with both acute and chronic inflammation? It has a short half-life of 19 hours (Vigushin *et al.*, 1993). CRP is not an indicator of malnutrition but many studies reported that serum albumin and pre-albumin were correlated negatively with hs-CRP during an acute phase response, thus hs-CRP was helpful in determining the levels of other visceral proteins (Kushner *et al.*, 2006).

2.3.3 Anthropometry

Anthropometry is a semi-quantitative quantification of body compartments such as bone, fat, and muscle. Anthropometric assessment includes the measurement of skeletal frame size, skinfold thickness (fat mass), body weight, height and mid-arm muscle circumference (muscle mass) (Woodrow *et al.*, 1996). Body mass index (BMI) is calculated from patients height and weight. BMI is used for assessment of obesity and malnutrition. BMI less than 18 kg/m^2 was considered as malnutrition, but should not be used alone as an indicator of nutritional status (Woodrow *et al.*, 1996).

Problem: Increasing risk of malnutrition-inflammation complex syndrome in ESRD patients on hemodialysis maintenance therapy.

Objective: The study aimed to:

1- *Measure and compare serum albumin, pre-albumin, and transferrin as markers for malnutrition in cases versus control groups.*

2- *Measure and compare serum hs-CRP, fibrinogen, albumin, and transferrin to assess acute inflammatory response in cases versus control groups.*

3- *Correlate study parameters with BMI, duration of dialysis, Age and hs-CRP in CKD group.*

4- *Determine the prevalence of chronic renal failure related to age, gender, and causative disease.*

3. Materials and Methods

This is a case-control study conducted at Alafia Hospital Hun-Aljufrah from December 2014 to December 2015. Libyan patients with ESRD who routinely attend to dialysis center at the above-mentioned hospital during the period of the study were randomly recruited for this study. The study included one hundred ESRD patients on regular hemodialysis maintenance therapy and one hundred age and sex-matched healthy controls, the sample size was derived by using the Fleiss formula for cross-sectional study using the following information (Fleiss, 1981)

Confidence interval = 95%, power of study = 80%, the ratio of cases to control of 1:1, the percentage of control exposed: 8.7% and percentage of cases exposed: 26%, this formula gave a minimum sample size of 75 for cases and 75 for control .

None of the participants suffered from any symptoms of infections or presented with clinical signs of infection (Hepatitis B, Hepatitis C, and HIV), malignancy, congestive heart failure, and active immunological disorders and they did not receive any medications known to affect immune functions and Overhydrated patients or patient with ascites or eclampsia were excluded from the study. The patients' information such as age, sex, height, weight, and clinical history were recorded. Blood samples (6ml) were collected from patients in plain containers from which serum is separated for various measurements. Serum albumin was measured by Bromo-cresol green method using spectrophotometer (Germany).CRP was measured by sandwich Enzyme-Linked Immunosorbent Assay using Stat Fax Microstrip Reader (Awareness Technology, USA). BMI calculated from a subject's height and weight.

4. Statistical analysis

The student's t-test was employed to compare differences between the mean concentration of study parameters and Pearson's

correlation for the association between study variables. P-value=0.05 indicating the difference was statistically significant. Data were analysed by SPSS (Version 16.0; SPSS Inc).

5. Result

This is a case-control study, included 100 patients with ESRD, 54% of them were males and 46% were females, their ages ranged between 16-81 years and the mean age was 43 years (Fig. 2). The results obtained revealed that hypertension was the primary cause of CKD (35.0% of respondents) while diabetes mellitus accounted for 30.0% of cases. However, UTI and glomerulonephritis were identified to be the primary cause in 8.0% and 7.0% of cases, respectively. Other identified causes, were Lupus Nephritis (4.0%), Polycystic Kidney Disease (3.0%), Gout (4.0%), Renal Stone (5.0%) and Obstructive Uropathy (4.0%) (Fig. 3).

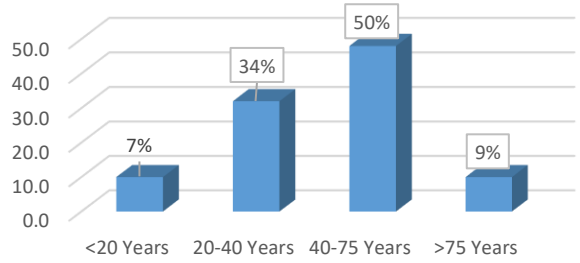

Fig. 2. Age distributions among patients with End-Stage Renal Disease.

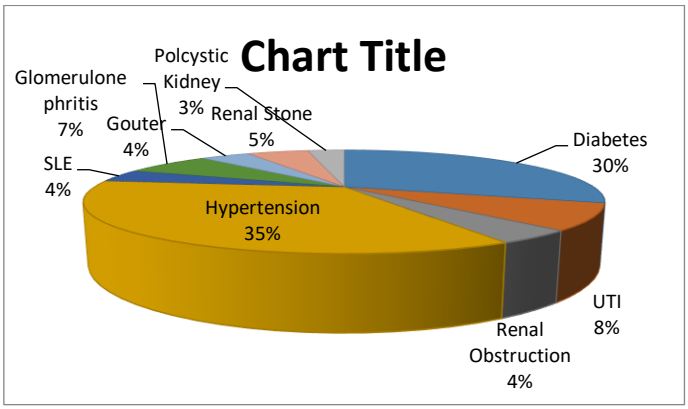

Fig. 3. Causes of End-Stage Renal Disease.

The result in Table 1 showed that the mean of albumin level (3.116 g/dl) was lower in a case group when compared to the control group (4.70 g/dl) with a significant difference between the two groups (p. value=0.000). The result in Table 1 also showed that the mean level of the CRP level (20.13 mg/dl) was higher among CKD patients when compared to the control group (3.22 mg/dl) with a significant difference between the two groups (p. value=0.000). Furthermore, the result in Table 1 showed that the mean level of BMI 20.3 Kg/m^2 was lower among CKD patients when compared to the healthy control group 26.1 Kg/m^2 with a significant difference between the two groups (p. value =0.049).

Table 1

Levels of albumin, BMI and CRP in CKD patients group and control group.

Study group / Parameters	CKD patients (Case group)		**Healthy Individuals (Control group)**		
	Mean	SD	Mean	SD	P. value
Albumin g/dl	3.116	0.3897	4.703	0.3883	0.000
CRP mg/dl	20.13	5.704	3.22	1.277	0.000

6. Discussion

Chronic kidney disease is a dynamic disease governed by multiple factors that affect its progression and prognosis. The prevalence of dialysis-treated ESRD was 624 per million populations (Wiam *et al.*, 2012). The principal aim of this study was to assess the association of Malnutrition-Inflammation Complex Syndrome in hemodialysis ESRD patients. The finding of this study showed that malnutrition in CKD patients on maintenance hemodialysis might be at risk of developing malnutrition which confirmed by the reduction in the mean serum level of albumin among the ESRD patients when compared to the control group and our findings were similar to those reported by Sathishbabu *et al.*, 2013 who reported that there was a reduction in serum albumin level and other biochemical protein parameters of malnutrition in hemodialysis patient. Our findings reported that the BMI levels were decreased among case group when compared to the control group and these findings were in agreement with the study done on Saudi patients conducted by Alharbi *et al.*, 2012 who showed that Malnutrition is Prevalent among Hemodialysis Patients. Furthermore, the present study correlated the level of serum with the level of the acute phase proteins CRP to link between malnutrition and systemic inflammation. The results obtained revealed that there was a significant negative correlation between albumin with hs-CRP and these findings were agreed with results published by Kelleher *et al.*, 1983 who reported that British ESRD patients had a significant negative correlation between plasma proteins markers of malnutrition and hs-CRP. Our findings support the fact that Albumin and prealbumin were negative acute-phase proteins their level tends to decrease during inflammation; also, the chronic inflammation is the main cause of malnutrition in ESRD patients. The correlation analysis showed that serum hs-CRP was correlated negatively with Albumin (r=-0.471, p-value=0.000) (Fig. 4).

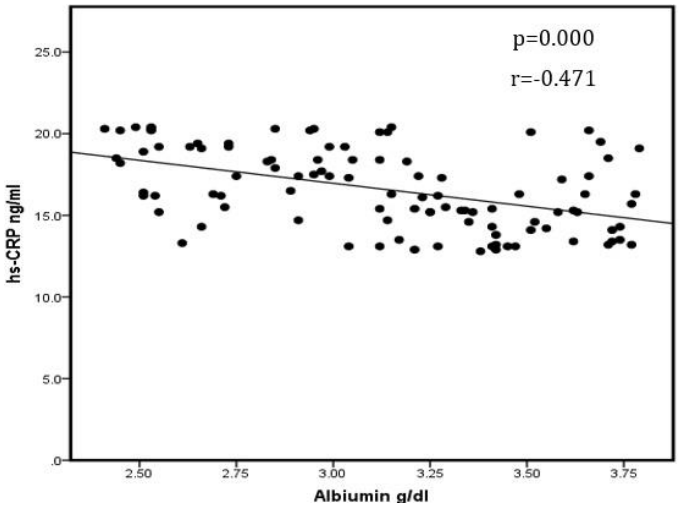

Fig. 4. Dot blot regression between hs-CRP level and Albumin among ESRD patients.

7. Conclusion

The significant decreased in the mean level of serum albumin and BMI, as well as the significant increase in the mean level of serum C-reactive protein among hemodialysis ESRD patients, might place them at risk of developing Malnutrition-Inflammation Complex Syndrome in the future. The significant negative correlation between serum albumin with hs-CRP support the facts that systemic inflammation is the main cause of malnutrition and cardiovascular disease in ESRD patient.

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