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Frequency and Relation of Malnutrition and Inflammation to Atherosclerosis Syndrome in Hemodialysis Patients in Zagazig University Hospitals

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Abstract: ***Background**: cardiovascular disease (CVD) still remains the main cause of morbidity and Mortality in maintenance hemodialysis (HD) patients, despite the considerable improvements in dialysis technology. Protein-energy malnutrition and inflammation are common in hemodialysis (HD) patients and these conditions' markers as hypoalbuminemia and elevated hs-C-reactive protein (CRP) have been described as predictive factors of cardiovascular mortality. Inflammatory mediators can induce anorexia, muscle proteolysis, low albumin synthesis, and also contribute to atherogenesis. **Objective**: to assess the frequency and relationship between malnutrition and inflammation to atherosclerosis in CRF patients under hemodialysis. **Patients and Method**: The study was performed on 100 non smoker subjects divided into two groups: (1) Patient Group consisted of 50 ESRD patients (24 males, 26 females, mean age: 46.1 ± 14.08 years) treated with regular HD for > 6 months, in the dialysis unit, Zagazig University. They were recruited for the study from January to June 2013.(2) Control Group consisted of 50 healthy subjects (24 males, 26 females, mean age: 41.66 ± 13.73 years).. To all subjects the following was done: I- Clinical examination: includes detailed history taking with special stress on duration of HD, ischemic heart disease, cerebrovascular or peripheral vascular insufficiency. II-Laboratory Investigations as complete blood count, FBS,P+PBS,hs CRP,liver and kidney function. III- Modified Subjective Global Assessment - Dialysis Malnutrition Score: Assessment of the nutritional status using Modified Subjective Global Assessment - Dialysis Malnutrition Score which consists of seven Features. IV- B-Mode Ultrasonography of the Common Carotid Arteries. **Results**: This study shows higher frequency of malnutrition (46%), inflammation (52%), and carotid plaques (48%) in HD patients. The serum creatinine, subjective global assessment – dialysis modified score (SGA-DMS), hs-CRP and carotid IMT (0.78 ± 0.21 mm) were significantly higher in patients compared with controls while the serum albumin was significantly low in patients compared with controls. Age was positively correlated with IMT and creatinine. Serum creatinine was positive correlation with IMT, hs-CRP and subjective global assessment – dialysis modified score SGA-DMS while serum albumen negatively correlation with all parameters. Hs-CRP and SGA-DMS was positively correlation with IMT. **Conclusions**: CRF on HD have higher frequency of malnutrition, inflammation, and carotid plaques and there is strong association of malnutrition and inflammation with atherosclerosis in this subjects Therefor we recommend good nutrition and management of inflammation to decrease occurrence of atherosclerosis and subsequent reduction of cardiovascular events.*

Keywords: inflammation, malnutrition, atherosclerosis, Hemodialysis, Zagazig, Responding author; Nafesa M. Kamal TEL N ; 01005618371

1. Introduction

Healthy subjects, as well as CKD patients who have not reached ESRD, are usually able to maintain neutral nitrogen balance with lower levels of protein intake if energy intake is adequate. In an advanced CKD or ESRD patients **Fouque, (2008)**, uremic malnutrition is present in approximately 20% - 50% of dialysis patients with reduced bioavailability of insulin like growth factor (IGF)-1when the GFR is less than 50 ml/min leading to impairments of glucose oxidation, the defective suppression of endogenous glucose production, with abnormal insulin secretion leading to hyperglycemia, hyperinsulinemia and hyperlipidemia **Rigalleau, (2005)**.

Reactive oxygen species (ROS)can be produced from leukocytes activated by contacting with the dialysis membrane as activated the complement system, and from erythrocyte iron released due to hemolysis, Intravenous administration of iron .All contribute to the inflammatory process and atherosclerosis in HD patients. nutritional and inflammatory markers are closely linked to CVD in ESRD. Taken together, there seems to be a vicious circle of malnutrition, inflammation and atherosclerosis in ESRD patients **Stenvinkel (2001)**.

2. Aim of the Work

Assessment the frequency and relationship of malnutrition and inflammation in patients on maintenance hemodialysis to atherosclerosis.

3. Subjects and Method

Case control study has been performed on 100 persons at zagazig university hospital hemodialysis and nephrology units, with informed consent and local ethical committee approval,who were categorized into two groups:

(1) Patient Group consisted of 50 ESRD patients (24 males, 26 females, mean age: 46.1 ± 14.08 years) treated with

regular HD for > 6 months, in the dialysis unit, Zagazig University. They were recruited for the study from January to June 2013.

(2) Control Group consisted of 50 healthy subjects (24 males, 26 females, mean age: 41.66 ± 13.73 years). **Inclusion Criteria:** All Adult ambulatory patients on hemodialysis for at least six months. The dialysis schedule consisted of three weekly sessions. **Exclusion criteria:** Excluded the presence of any of the following: pregnancy, tobacco smoking, diabetes mellitus, liver diseases, heart failure, malignancy, acquired immunodeficiency syndrome (AIDS), evident acute infection, connective tissue diseases or patients receiving drugs that may modify the immune response like corticosteroids. **To all subjects** the following was done:

I- Clinical examination like blood pressure and peripheral pulsation**. II- Laboratory Investigations:** The following investigations were done in serum samples: · Creatinine. · Albumin. · High sensitivity CRP: measured by ELISA,CBC,FBS,PPBS ,lipid profile, serum calcium and phosphorus. For HD patients, blood samples were taken immediately before the HD session. **III- Modified Subjective Global Assessment - Dialysis Malnutrition Score:** Assessment of the nutritional status using Modified Subjective Global Assessment - Dialysis Malnutrition Score which consists of seven features; weight change, dietary intake, GI symptoms, functional capacity, co-morbidity, subcutaneous fat and signs of muscle wasting. Each component has a score from 1 (normal) to 5 (very severe). Thus the malnutrition score (sum of all seven components) is a number between 7 (normal) and 35 (severely malnourished). Lower score denotes tendency towards a normal nutritional status. A higher score is considered to be an indicator of the presence of malnutrition elements i.e. protein energy malnutrition. **IV- B-Mode Ultrasonography of the Common Carotid Arteries:** The intima media thickness (IMT) on each side was measured as the distance between intimal luminal interface and medial- adventitial interface and the mean was calculated.

Consenting; All the participates in the research had consented to the procedure after complete explanation of the steps, the objective and nature of the research.

4. Results

Table 1: Baseline data of the studied groups

	Case	Control	P
Gender male/female	24/26	24/26	1.0
Age(years)X±SD	46.1±14.08	41.68±13.73	0.09
S.Creatinine(mg/dl)	9.4±2.96	0.71±0.16	< 0.001
S.Albumin (gm/dl)	3.65±0.74	4.0±0.41	< 0.005
SGS-DMS	17.98±8.43	8.78±2.25	< 0.001
Hs-CRP(mg/dl)	7.98±2.25	3.31±1.42	< 0.001
RT IMT(mm)	0.78±0.21	0.6±0.09	< 0.001
LT IMT(mm)	0.74±0.18	0.68±0.08	< 0.001

Table (1)showed that no significant difference between patients and controls as regarding the age and sex but the serum creatinine, subjective global assessment – dialysis modified score (SGA-DMS), hs-CRP and caroted IMT were significantly high in patients compared with controls while the serum albumin was significantly low in patients compared with controls .

Table 2: Frequency of malnutrition, inflammation and atheromatous plaque in hemodialysis patients.

	N	%
Frequency of malnutrition in hemodialysis patients.	23	46.0%
Frequency of inflammation in hemodialysis patients.	26	52.0%
Frequency of atheromatous plaque in hemodialysis patients.	24	48.0%

Table (2): showed that Frequency of malnutrition(46.0%),inflammation(52%) and atheromatous plaque(48%) in hemodialysis patients.

Table 3 : Correlation matrix between different studied parameters among hemodialysis patients.

	IMT	SGA-DMS	Hs-CRP	Albumine	Creatinine
Age(years)	0.357*	0.113	0.320	0.345*	0.564*
S.Creatinine (mg/dl)	0.839**	0.791**	0.817**	0.624**	---
S.Albumin (gm/dl)	0.579**	0.566*	0.529*	---	---
Hs-CRP(mg/dl)	0.751**	0.725**	---	---	---
SGS-DMS	0.7**	---	---	---	---

Table (3): showed that age was positively correlated with IMT and creatinine. serum creatinine was positive correlation with IMT, hs-CRP and subjective global assessment – dialysis modified score SGA-DMS while serum albumen negatively correlation with all parameters. hs-CRP and SGA-DMS was positively correlation with IMT.

* mean P- Value < 0.05
**mean P- Value < 0.001

Table 4: Relation between atheromatous plaque and different parameters.

Parameter mean±SD	With plaque(N:24	Without plaque(N:26)	P
Age(years)	48±12.4	44±13.1	< 0.05 S
S.Creatinine (mg/dl)	11.0±3.4	7.8±2.4	< 0.001 HS
S.Albumin (gm/dl)	3.1524±0.24211	4.02±0.78166	< 0.001 HS
SGA-DMS	24.476±7.0329	13.275±5,87912	< 0.001 HS
Hs-CRP (mg/dl)	10.314±1.5473	6.300±2.1352	< 0.001 HS
IMT(mm)	1.0048±0.1244	0.6310±0.1072	< 0.001 HS

Table (4): showed that patients with atheromatous plaques were significantly older and more often had a high CRP, low serum albumin levels and evidence of malnutrition than others without atheromatous plaques .

5. Discussion

Despite the considerable improvements in dialysis technology, nontraditional risk factors such as inflammation and malnutrition are the most frequent chronic complications may contribute to an increased cardiovascular mortality among dialysis patients **Stenvinkel (2001).**

High prevalence of malnutrition (46%), inflammation (52%) and atherosclerosis (48%) was observed in the present study. These finding is concordances with **Afsaret et al., (2006)** who shown that inflammatory processes are common in dialysis patient as reflected by increased inflammatory marker in approximately 30% to 60% of dialysis patients and also **Perunicic-Pekovic et al., (2004)** who said that patients on maintenance hemodialysis (HD), malnutrition is frequent and affects on quality of life and is associated with increased risk of mortality and morbidity.

Hypoalbuminemia increase plasma lipoprotein (a), oxidant/antioxidant imbalance and platelet aggregability leading to atherosclerosis. Alternatively, malnutrition may occur as a complication of advanced atherosclerotic cardiovascular disease **Fernandez-Reyes et al., (2002)**.

Alternatively, malnutrition is associated with a parallel degree of impairment of all immune system functions. This will favor persistence of chronic, possibly unrecognized infections, which constitute a significant cause for chronic microinflammation in HD patients **Minnaganti et al.,(2008)** .And vise versa, proinflammatory cytokines may cause malnutrition by acting directly on the gastrointestinal system or indirectly through affecting appetite and resting energy expenditure **Minnaganti and Cunha. (2008) .**

This study shows there was statistical significant decrease serum albumin in patients compared with controls. Also hypoalbuminemia is a confirmed predictive factor for cardiovascular morbidity and events in chronic kidney disease patients of advanced disease stages **Shah et al., (2008)**.

These results were agreed with **Zimmermann et a**l., **(2004).**who showed that patients who had serum albumin values below 40 g/l were significantly more likely to die due to cardiovascular reasons, compared to those having serum albumin values over this cut off (34% vs. 6%, respectively) . And **Perunicic et al., (2004)**,who said that patients on maintenance hemodialysis (HD), malnutrition is frequent and affects on quality of life and is associated with increased risk of mortality and morbidity.

Detsky et al.,(1987),. deffine special methodology, named SGA which was designed to circumvent many of these problems. It is easy to use and consists of only three discrete severity levels but closely correlated with more subjective measures. Unfortunately final assessment of each SGA criterion is solely depends on the subjective impression of the evaluator. Subjective global assessment – dialysis malnutrition score (SGA-DMS) is more objective than the SGA.

We, as well as **Kalantar-Zadeh et al.,(2003),** found that (SGA- DMS) was not significantly correlated with age but significantly correlated with C- reactive protien. There is a negative correlation between SGA with serum albumin

Inflammation and dietary protein intake exert competing effects on serum albumin levels **Kaysen et al., (2001)**. Albumin is suppressed when hepatic protein synthesis switches to the production of acute phase proteins (APP) **Heimburger et al., (2000)**.

Even if several factors initially released at the site of inflmmation by activated phagocyte mononuclear cells and lymphocytes are able to enhance the transcription of the CRP gene in the hepatocyte. Serum hs-CRP is commonly employed to define the presence of acute phase response or inflammatory reaction **K/DOQI (2005)**.

Our study shows statistically significant increase of hs- CRP in CRF patients in relation to controls(P—0.001),Also serum hs-CRP showed a statistically significant positive correlation with carotid IMT and negatively correlated with serum albumen.

This result were consistant with **Kir et al., (2012).** whom noticed that having higher CRP levels in hemodialysis patients is associated with higher morbidity and cardiovascular mortality. Several lines of evidence indicate that inflammation plays an important role in the initiation and progression of atherosclerosis, which is nowadays considered an inflammatory disease **Ross et al., (2005)**. Also **O'Leary and Polak,. (2002)** who said that atheromatous plaques were detected in 24 (48%) patients and Carotid IMT was significantly higher in HD patients (0.78 ± 0.21 mm) compared with controls (0.6 ± 0.09 mm, P = <0.001). Also **O'Leary and Polak., (2002)** who said that Carotid IMT is strongly associated with coronary atherosclerosis and is an independent predictor of CVD events after adjustment for traditional risk factors.

This result were goes hand by hand with **Stenvinkel et al., (2005)** who said that elevated levels of pro inflammatory cytokines may cause malnutrition by acting directly on the gastrointestinal system or indirectly through affecting appetite and resting energy expenditure. And also **Kaysen (2003)** who said that inflammation induce an acute phase response in the liver resulting in decreased rate of albumin synthesis and increased rate of degradation. Several lines of evidence indicate that inflammation plays an important role in the initiation and progression of atherosclerosis, which is nowadays considered an inflammatory disease **Ross (2005)**.

In the present study, Patients with atheromatous plaques were significantly older in age compared to patients without atheromatous plaques (48±12.4vs 44±13.1 years, respectively, P < 0.05. There was a statistically significant positive correlation between age and carotid IMT (0.357*). Also, carotid IMT is strongly correlated with the age of the patients, SGA-DMS and hs-CRP.

These results goes hand by hand with **Nassiri et al., (2012)** who reported that age, high sensitive C-reactive protein had a significant correlation with the mean CIMT. It is well known that advancing age is the most powerful cardiovascular risk factor. Also This study in harmmony with **McDermott,. (2007)**.who said that the prevalence and incidence of cardiovascular disease increases exponentially with age.

6. Conclusion and Recommendation

This study is one of the few studies to show high frequency of malnutrition (46%), inflammation (52%), and carotid plaques (48%) in chronic hemodialysis patients and showed that chronic kidney diseased patients on maintenance hemodialysis have a strong association between malnutrition, inflammation and arthrosclerosis. So we can concluded that use malnourished HD patients are often older and have an enhanced acute phase response. These results suggest that low serum albumin level and elevated CRP levels are highly assossiated with an increased carotid IMT in HD patients.

So we recommend that good nutrition and good management of inflammation to decrease occurrence of atherosclerosis and atheromatous plaques, Also recommend using Modified Subjective Global Assessment –Dialysis Malnutrition Score as a nutritional assessment tool for CKD patients in both the clinical and research settings.and hs-CRP as a predictor of inflammation in HD patients.

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