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Research article

Malnutrition, inflamation and atherosclerosis (MIA syndrome) in patients with end stage renal disease on maintenance hemodialysis (a single centre experience)

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ABSTRACT

Background: Inflammation and malnutrition play an important role in endothelial dysfunction, atherosclerosis and excessive cardiovascular morbidity and mortality in ESRD patients
Aim of the study: The primary objective is to determine the prevalence of inflammation, malnutrition and atherosclerosis in patients on maintenance haemodialysis. Secondary objective was to determine the association for atherosclerosis with inflammation and malnutrition.
Patient and methods: One hundred and one adult patients with end stage renal disease on maintenance haemodialysis who are met with the exclusion criteria were enrolled in this cross sectional study from haemodialysis unit of Baghdad teaching hospital over the period of July/2015 – June 2016. All patients were thoroughly examined and many variables were evaluated (age, gender, blood pressure, diabetes mellitus, serum lipid profile, smoking habits, serum albumin, CRP, calcium, Phosphate, Parathyroid hormone and haemoglobin measurements). All patients underwent a carotid Doppler ultrasound study.
Results: Atherosclerosis was present in 65.3%: 58.4% of patients had malnutrition and 43.6% had inflammation. The association for atherosclerosis and high CRP and low serum albumin is strong and independent of other atherosclerosis risk factors. There is significant inverse and independent correlation between CRP and albumin.
Conclusion: Inflammation (high serum CRP) and malnutrition (low serum albumin) in patients on haemodialysis are significantly associated with carotid atherosclerosis. Inflammation was more prevalent in the malnourished patients than in those with normal nutritional status.

1. Introduction

The pathogenesis of cardiovascular damage to haemodialysis patients is far more complex than in the general population [1]. The causes of atherosclerotic CVD in ESRD patients is probably multifactorial [2]. There is definitely a high prevalence of traditional risk factors like HTN, DM and lipid disorders in chronic kidney disease patients [3], but this alone cannot explain the existing high burden of CVD in this population [4,5]. Thus, it has been postulated that non-traditional risk factors, such as malnutrition, oxidative stress and inflammation, may be more important [6,7]. Factors such as inflammation and malnutrition may cause serious complications and increase mortality rate in dialysis patients [8,9].

However, it should also be pointed out that the association for chronic inflammation and CVD may also be indirect [10], as chronic inflammation has been shown to be associated with endothelial dysfunction, insulin resistance and increased oxidative stress, all believed to cause atherosclerosis [11]. Normal endothelial function is important to maintaining cardiovascular homeostasis; therefore, endothelial injury may result in lipid accumulation, smooth muscle proliferation, and vasospasm [12]. Oxidative stress has been recognized as an important factor of the development of both endothelial dysfunction and atherogenesis [13,14]. An increased carotid intima media thickness (CIMT) is regarded as an early sign of atherosclerosis [15]. CIMT is related to cardiovascular disease affecting distant vascular beds such as cerebral, peripheral, and coronary artery vascular beds [16]. Moreover, increased CIMT might be an independent predictor of cardio- vascular mortality in the haemodialysis population [17–21], A CIMT more than 0.9 mm has been shown to be a marker of generalized atherosclerosis and is associated with cardiovascular risk factors [22].

High resolution B-mode ultrasound scans for the carotid arteries provides measures of CIMT and atherosclerotic plaques.

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It is a reliable, reproducible, non- invasive, inexpensive, and easily available method [23].

Uremic toxin accumulation like Advanced Glycation End products (AGEs) caused by decreased renal clearance might promote inflammation [24]. A correlation has been found between one AGE, Pentosidine, and CRP [25].

Dialysis-related factors, such as bio-incompatibility between blood and dialyzer, the presence of endotoxin in dialysis fluid and access-related infections, have been implicated in feeding the inflammation cycle in ESRD patients [26–30].

Available evidence suggests that C-reactive protein (CRP) is a precise objective index of the inflammatory activity and that it accurately reflects generation of pro-inflammatory cytokines, such as interleukin (IL)-6 and Tumor necrosis factor-a (TNF-a) [31,32]. CRP is widely considered as a marker for underlying inflammatory processes of ESRD [33].

Protein energy malnutrition is a common phenomenon in maintenance haemodialysis patients, Its reported prevalence varies from 18% and 75% in dialysis patients [34–36].

Hypoalbuminemia, a marker for malnutrition and underlying inflammation, has come up as a powerful predictor of mortality in patients with ESRD [37] and also a significant predictor for the occurrence of denovo vascular events in this population. In dialysis patients, the HEMO study demonstrated that serum albumin is closely associated with the prevalence of CAD [38]. Cai and colleagues have implied serum albumin as potential scavenger of free radicals. Decrease in serum albumin level would lead to decrease antioxidant capacity and favour the noxious effects of oxidative stress on a variety of tissues, including the arterial vessel wall [39]. One possible explanation may be the strong documented interactions between atherosclerotic CVD and inflammatory as well as nutritional parameters in ESRD patients [40,41]. This strong association with malnutrition, inflammation, and atherosclerosis in this patient population suggesting the presence of a syndrome called malnutrition, inflammation, and atherosclerosis (MIA) [42,43] which is associated with an exceptionally high mortality rate [43,44]. Cano et al. [45] have reported that on 20–60% of haemodialysis patient may have malnutrition inflammation complex [46].

We need new treatment strategies of the inflamed ESRD patient. The use of both biocompatible membranes [47,48] and ultrapure dialysate [49] has been shown to reduce various inflammatory parameters, and haemodialysis patients with inflammation should thus be treated with biocompatible membranes and ultrapure dialysate.

Anti-inflammatory therapy: Angiotensin-converting enzyme (ACE) inhibitors, in addition to their renal protective effects, showed anti-inflammatory properties in end-stage renal disease [50]. ACE inhibitors may suppress production of cytokines, such as TNF-a & IL-1b, both in vitro [51] and in vivo [52] in mice. Moreover, the use of ACE inhibitors in pre-dialysis patients have been shown to be associated with lower TNF-a and CRP levels [53]. L-Carnitine supplementation in haemodialysis patients significantly reduced serum CRP, through yet unknown mechanism(s) [53]. The reported effects of statins on inflammatory biomarkers in ESRD are not as consistent in JUPITER trial treatment for Rosuovastatin lead to a 37% decrease of CRP levels which was associated with significant reductions in cardiovascular events and all-cause mortality [54]. In the AURORA study 2776 dialysis patients were treated with Rosuvastatin versus placebo and were followed for 3.6 years, No significant differences in the incidence of cardiovascular events between the two groups were noted during the follow-up period [55].

Supplementation with vitamin E decreases CRP [56,57] and monocyte IL-6 levels [56] in non-renal patient groups, also vitamin E has been shown to decrease the oxidative susceptibility to low-density lipoprotein [58] and to reduce cardiovascular end points in haemodialysis patients [59]. Enteral and intradialytic parenteral nutrition seems promising to improve nutritional status and reduce inflammatory cytokines, however it still needs further exploration [60].

2. Patients and method

One hundred and one adult patients with end stage renal disease on maintenance haemodialysis who are met with the exclusion criteria were enrolled in this cross sectional study from haemodialysis unit of Baghdad teaching hospital over the period of July/2015 – June 2016. all patients were thoroughly examined and many variables were evaluated (age, gender, blood pressure, diabetes mellitus, serum lipid profile, smoking habits, serum albumin, CRP, calcium, phosphate, PTH, and haemoglobin measurements), All patients underwent a carotid doppler ultrasound study. All patients enrolled in this study had been on haemodialysis for at least 3 months and were clinically stable. Patients with active infection, liver disease, autoimmune diseases or malignancies were excluded, in order to avoid the possible effects of these co-morbid conditions on cytokine production. Informed consent was obtained from all the study patients.

`Hypoalbuminemia was defined as serum albumin <4 g/dl according to National kidney foundation- disease outcome quality initiative guideline (NKF-DOQI). Nutritional status was assessed by serum albumin as several studies have demonstrated that serum albumin is a valid indicator of nutritional status in haemodialysis patients . According to the (NKF-DOQI), serum albumin equals to or greater than 4 g/dl is the outcome goal for haemodialysis patients [61].

The presence of inflammation was assessed by c reactive protein (CRP), available evidence suggests that CRP is a precise objective index of the inflammatory activity and that it accurately reflects generation of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumour necrosis factor-a (TNF-a) [24,25]. Serum CRP levels were evaluated by traditional (standard) CRP assay, using commercially available CRP kit. Serum CRP more than 3 mg/ls was considered high as defined in guideline on the centres of disease control and prevention and the American heart association [62].

All patients underwent a carotid doppler ultrasound study, evaluating the common carotid, bifurcation and the origin of the internal carotid artery, analysing the presence of plaques, in addition to measuring the carotid intima media thickness (IMT) [63]. We calculated the average of 8 measurements, right and left, considering an IMT less than 0.9 mms as a normal value, according to the criteria of the European guidelines on hypertension of the ESC-ESH [64]. An atherosclerotic plaque was defined as a local thickness of intima greater than 1 mm [65]. Abnormal IMT and/or plaque occurrence in the carotid arteries were used as indicators of carotid atherosclerosis as in previous studies in the general population as well as in studies involving patients with ESRD [66].

Smoking was considered to be present if the patient currently smokes more than ten cigarettes per day. Dyslipidemia was defined according to adult treatment panel (ATP) III of the national cholesterol education program that considered dyslipidemia is present if the patient has any of the following (serum LDL-C > 100 mg/dl, HDL-C < 40 mg/dl in male and <50 mg/dl in female, serum triglyceride >150 mg/dl, total serum cholesterol >200 mg/dl). Diabetes mellitus was defined as random blood glucose concentration ≥200 mg/dl or fasting blood sugar ≥126 mg/dl 113 or patients were considered diabetics when they had prior diagnosis of diabetes.

Hypertension: systemic arterial hypertension was defined as systolic arterial pressure ≥140 mmHg and/or diastolic arterial pressure ≥90 mmhg or currently using antihypertensive drugs to control the blood pressure [67].

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