
Inflammatory Cytokines and Malnutrition as Related to Risk for Coronary Heart Disease in Hemodialysis Patients

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Abstract

Background. Malnutrition and inflammation are associated with end-stage renal disease (ESRD). Interleukin (IL)-6 and tumor necrosis factor- α (TNF- α) powerfully predict death from cardiovascular disease.

Aim of our study was to establish association between markers of inflammation and parameters of malnutrition in hemodialysis patients.

Methods. The study population consisted of 42 hemodialysis patients with different parameters of malnutrition and mean age 55 ± 8 with dialysis duration $6,25 \pm 2$. Blood samples were taken after an overnight fast and plasma lipid profiles were measured: total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, using conventional enzymatic methods. Serum urea and creatinine levels were also measured by the routine procedures of our laboratory. Inflammatory cytokines, IL-6 and TNF- α , and parathyroid hormone were measured by photometric enzyme-linked immunosorbent assay (ELISA). We used standard Doppler echo examinations to determine of left ventricular mass index (LVMI).

Results. Malnourished patients had significantly increased cardiovascular disease and carotid plaques. Significant positive relations between TNF- α and LDL/HDL cholesterol was found in the groups ($p < 0.05$) and positive correlation between IL-6 and LVMI ($p < 0.05$).

Conclusions. In summary, this cross-sectional study in hemodialysis patients has demonstrated a high prevalence of malnutrition, inflammation, carotid plaques and cardiovascular disease. Malnourished dialysis patients are more often with cardiovascular disease and carotid plaques and have elevated inflammatory cytokines which all may increase the risk of atherosclerotic vascular disease.

Key words: inflammatory cytokines, lean body mass, cardiovascular disease, hemodialysis

Introduction

Malnutrition and inflammation are associated with end-stage renal disease (ESRD). Interleukin (IL)-6 and tumor necrosis factor- α (TNF- α) powerfully predict death from cardiovascular disease in dialysis patients as well as progression of vascular injury (1,2,3). Atherosclerosis and inflammation have similar basic mechanisms involving the adhesion of leukocytes to vascular endothelium in their early

phases. Major predictors of clinical outcome in dialysis patients are protein-energy malnutrition (PEM) and inflammation (4,5,6). A common mechanism for the development of cardiovascular disease and malnutrition in dialysis patients may be cytokine activation (7,8,9,10).

The total concentration of serum non-esterified fatty acids (NEFA) plays an important role in the pathogenesis of cardiovascular disease (CVD). Individual circulating NEFA have achieved less scientific focus in relation to atherosclerosis compared to total NEFA. A strong link exists between chronic inflammation and nutritional markers in hemodialysis (HD) patients. Biological effects of n-3 fatty acids have been shown in studies of animals and humans in which anti-inflammatory and antithrombotic effects could be of relevance in HD patients (11,12).

N-3 long chain polyunsaturated fatty acids (n-3 LC-PUFA), mainly eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), are present in tissues both from endogenous synthesis from desaturation and elongation of 18:3 n-3 and/or from dietary origin (marine products and fish oils) (13).

Markers of inflammation, nutritional status and insulin resistance as etiologic factors participate a grate deal in premature atherosclerosis. Chronic kidney disease is associated with plasma fatty acid patterns similar to those that occur when there is nutrition deficiency of essential fatty acids (14,15,16).

Aim of our study was to establish the association between markers of inflammation and atherosclerosis with parameters of malnutrition in hemodialysis patients.

Patients and methods

The study population consisted of 42 hemodialysis (HD) patients with different parameters of malnutrition and mean age 55 ± 8 with dialysis duration $6,25 \pm 2$. Patients were divided according to tertiles of lean body mass (LBM) was assessed by bioelectrical impedance (BIA) and with the following intertertiles ranges: 1st tertile (LBM-37kg), 2nd (LBM 38-50kg) and 3rd (LBM ≥ 51 kg). For nutritional assessment simple parameters were used: triceps skinfold (TSF), midarm muscle circumference (MAMC), body mass index (BMI), and serum albumin concentration as representative of body fat, muscle protein and visceral protein respectively. Blood samples were taken after an overnight fast and plasma lipid profiles were measured: total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, using conventional enzymatic methods. Serum urea and

creatinine levels were also measured by the routine procedures of our laboratory. The fatty acid pattern of plasma and erythrocytes were examined by gas liquid chromatography. Inflammatory cytokines, IL-6 and TNF- α , was measured by photometric enzyme-linked immunosorbent assay (ELISA).

We used standard Doppler echo examinations to determine of left ventricular mass index (LVMI).

Results

The main results of the study show on the Table 1. HD patients of the 3rd tertile, representing 30% of the whole group, presented LBM levels indicative of a well nourished group. These patients presented BMI and other nutritional parameters, significantly higher than that of the patients in the 1st tertile. IL-6 and TNF- α were higher in the patients in the 1st tertile and these differences were significantly according to 3rd tertile. Patients with a lower LBM values had decreased BMI, MAMC, albumin and transferrin level than those in the higher tertile. Malnourished patients had significantly increased cardiovascular disease and carotid plaques.

Table 1. Comparison between HD groups according LBM tertiles

	1 st tertile	3 rd tertile	p
Number	14	16	
BMIkg/m ²	22±3.4	24±1.97	0.04
MAMCcm	23.9±4.7	25.7±3.1	0.04
Albuming/L	31±3.01	33±3.21	0.05
Transferin pg/ml	1.42±0.29	1.75±0.32	NS
TNF- α pg/ml	2.08±1.65	1.95±1.53	NS
IL-6 pg/ml	4.50±4.19	3.41±3.39	0.03
Carotid plaques %	62	39	<0.05
CVD %	89	72	<0.05

Significant positive relations between TNF- α and LDL/HDL cholesterol was found in the groups ($p < 0.05$) and positive correlation between IL-6 and LVMI ($p < 0.05$) Table 2 and Table 3.

Table 2. Correlation coefficient (r) between TNF- α and LDL/HDL-cholesterol concentration LDL/HDL-cholesterol

	1 st tertile		3 rd tertile	
TNF- α	r = 0.33	p < 0.05	r = 0.32	p < 0.05

Table 3. Correlation between IL-6 and LVMI in both group of HD patients

	r	p
LVMI	0.33	<0.05

There was correlation between serum albumin and docosahexaenoic acid-DHA (r 0.415 p= 0.05) and correlation between serum albumin and arachidonic acid – AA, r 0.643, p= 0.002) Table 4. There was correlation between diastolic blood pressure and PUFA (Table 5).

Table 4. Correlation between serum albumin level and PUFAs

Parameters	p	r
DHA er 22:6 (n-3)	0.05	0.415
AA er 20:4 (n-6)	0.002	0.643

Table 5. Correlation between diastolic blood pressure and PUFAs

Parameters	p	r
DHA er 22:6 (n-3)	0.05	-0.409
AA er 20:4 (n-6)	0.06	-0.411

Discussion

The accelerated atherosclerotic process of ESRD may involve several interrelated conditions, such as oxidative stress, endothelial dysfunction, vascular calcification, and inflammation. Studies in the general population and in ESRD patients have demonstrated a significant association between inflammatory markers and CVD (17,18,19).

In this study we have shown that HD patients had reduced PUFAs in the red cell phospholipid. This study has demonstrated high prevalence of malnutrition, inflammation, carotid plaques and cardiovascular disease. Malnourished dialysis patients are more often with cardiovascular disease and carotid plaques and have elevated inflammatory cytokines which all may increase the risk of atherosclerotic vascular disease.

Peck suggests that HD patients may have increased prostaglandin E2 (PGE2) values and fatty acid profiles indicative of EFAD. Sinzinger and Leitner have shown that the metabolism of arachidonic acid shifted from the cyclooxygenase pathway to the lipooxygenase pathway in renal patients. Higher level of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) block the lipooxygenase pathway of eicosanoid production, pushing the arachidonic acid metabolism to cyclooxygenase pathway. This pathway leads into increased level of prostaglandin E2 (PGE2) which acts less inflammatory than leukotriene B4 (20).

Phospholipids play a main role in the membrane function. The length and degree of unsaturated fatty acids are determinants of enzymes activity. The activation of peroxisome proliferator activated receptors (PPARs) might be a possible mechanism for down regulation of inflammatory markers with supplementation of n-3 fatty acids (21). Supplementation with n-3 fatty acids have been shown in many studies of animals and humans in which anti-inflammatory effects theoretically could be of relevance in patients with renal disease (22). These data indicate that PUFAs deficiency may be associated with increase inflammatory cytokines and their levels after treatment may reflect on better clinical outcome.

Conclusion

In summary, this cross-sectional study in hemodialysis patients has demonstrated high prevalence of malnutrition, inflammation, carotid plaques and cardiovascular disease. Malnourished dialysis patients are more often with cardiovascular disease and carotid plaques and have elevated inflammatory cytokines which all may increase the risk of atherosclerotic vascular disease. These data suggested that inflammatory markers in malnourished HD patients would identify patients at high risk of comorbidity and mortality. The degree of inflammation correlates with disease severity. Dietary regime with fish oil supplementation could be used in patients with chronic kidney disease in order to slow down atherosclerosis process and prevent cardiovascular events and progression of renal failure.

Experimental study report that short-term incubation of human endothelial cells with TNF α causes an essential fatty acids deficiency state described for long term malnutrition (23).

Yli-Jama et al investigated association between serum nonesterified EPA and DHA, and soluble vascular cell adhesion molecule-1 (sVCAM-1). Negative associations were found between sVCAM-1 and the serum levels of non-esterified DHA, EPA and AA. The inverse relation between the levels of sVCAM-1 and very long-chain n-3 fatty acids might indicate an anti-inflammatory effect of the later (24).

These results suggest that nutritional intervention strategies may improve the nutritional status of malnourished HD patients and thus possibly help to lower mortality rates.

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