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Elshamaa MF, Sabry S, Nabih M, Elghoroury EA, El-Saaid GS
Ismail AAG

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Alteration in Plasma Total Antioxidant Capacity, Cardiotoxic Lipid Peroxidation Product and C-Reactive Protein: A Possible Explanation for the Increased Cardiovascular Risk in Children on Hemodialysis

M. F. Elshamaa[1], S. Sabry[2], M. Nabih[2], E. A. Elghoroury[3], G. S. El-Saaid[4], A. A. G. Ismail[3]

Background: Patients with end-stage renal disease undergoing hemodialysis (HD) are exposed to oxidative stress, which is associated with an impairment of antioxidant defense and an overproduction of oxidative stress markers. Oxidative stress plays a significant role in the development of inflammation in these patients. Objectives: The high incidence of cardiovascular diseases in HD patients is now well established and the involvement of oxidative stress has been hypothesized in these phenomena. This study focused on a comparison of plasma total antioxidant capacity (TAC) and lipid peroxidation product and evaluated the relationship between them and high-sensitivity C-reactive protein in patients on HD. Subjects and Methods: Plasma (TAC), lipid peroxidation products, malondialdehyde (MDA) as well as high-sensitivity C-reactive protein were determined in 30 patients on HD and in 20 normal controls (NC). Results: TAC and MDA levels were significantly higher in patients on HD than in the control subjects ($p < 0.001$). The hs-CRP values were also significantly higher in patients than in the NC ($p < 0.001$). The percentage of HD patients with CRP > 10 mg/l was 30 %. The concentrations of TAC and MDA were positively correlated with hs-CRP in HD patients ($p < 0.08$, $r = 0.52$ and $p < 0.04$, $r = 0.75$, respectively). There were independent associations between hs-CRP level in the serum of HD patients and TAC concentration, MDA value, cholesterol concentration, Hb concentration and adequacy of dialysis by multiple linear regression analysis. Conclusion: Our study demonstrates an increase in oxidative stress in children on HD and that the susceptibility to oxidative stress is strongly related to the levels of MDA produced in plasma which is strongly indicative of the inflammatory status in HD patients. These profound disturbances in oxidative stress markers may provide an explanation for the cardiovascular complications in these patients. ***J Clin Basic Cardiol 2008; 11 (online): 2–7.***

Key words: *total antioxidant capacity, lipid peroxidation product, high sensitivity, c-reactive protein, hemodialysis*

Cardiovascular disease is the major cause of morbidity and mortality in patients with end-stage renal disease (ESRD) receiving renal replacement therapy [1]. Several factors may contribute to the greatly increased risk of atherosclerotic disease, including an increased prevalence of hypertension. In addition, patients with renal failure have an abnormal lipid profile characterized by reduced HDL cholesterol and moderate hypertriglyceridemia [2]. However, these factors by themselves are not sufficient to account for the excess cardiovascular disease observed.

Patients on hemodialysis (HD) are constantly exposed to oxidative stress [3–5]. This is mostly attributed to a bioincompatibility type of reactions, originating from the dialysis membrane and the imbalance between oxidants and antioxidants due to the diffusion of hydrophilic compounds to the dialysate. The intensity of oxidative stress in HD patients can be influenced by many factors among which are duration of dialysis therapy, primary cause of chronic renal failure (CRF), intensity of chronic inflammation, type of diet or environmental toxins [6–8].

One of the events that predominate in oxidative stress is the alteration of lipid metabolism, which is demonstrated by the oxidation of low-density lipoprotein plasma lipids and the release of short-chain aldehydes, such as malondialdehyde [9–11]. The increase in lipid peroxidation (LPO) in HD patients accompanied by the abnormal antioxidant defenses has a pathologic relevance in many diseases, in particular in those having an inflammatory component, such as atherosclerosis [7, 12–15]. Thus, it appears that in HD therapy, a synergism between oxidative stress and inflammatory response is developed. Plasma C-reactive protein (CRP) is considered a sensitive marker of induction of inflammatory activity in all patients treated with HD [13, 16, 17].

Aim of the Study

The present study attempts to look at the comparison of high-sensitivity CRP (hs-CRP) levels, the levels of total antioxidant capacity and serum lipid peroxidation product in HD patients, aiming to find a possible explanation for the increased cardiovascular risk in these patients.

Patients and Methods

Thirty patients with ESRD on regular HD therapy selected from the hemodialysis unit of the Center of Pediatric Nephrology and Transplantation in the Childrens Hospital, Cairo University, were included in this study.

The study was done in a period from December 2007 to April 2008. Of the patients examined 17 (56.67 %) were male and 13 (43.33 %) female, aged 10.53 ± 3.43 years (range 4–18 years). They were being treated with hemodialysis for 3–4 hours thrice weekly with polysulfone membrane using bicarbonate-buffered dialysate produced with ultrapure water of high bacteriological quality, blood flow rate ranged from 80–180 ml/min according to body weight, dialysate flow rate was 500 ml/min and did not change, heparin was used as an anticoagulant.

Inclusion criteria included children on regular HD treatment for at least three months. None of the patients had evidence of a systemic infection (fever or leukocytosis). Patients with known cardiovascular disease, chronic hepatitis, hema-

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From the [1]Pediatric Department, National Research Center, Cairo; [2]Pediatric Department, Faculty of Medicine, Cairo University; [3]Clinical & Chemical Pathology Department, National Research Center, Cairo; [4]Medical Biochemistry Department, National Research Centre, Cairo, Egypt.
Correspondence to: Manal F. Elshamaa, MD, Pediatric Department, National Research Center, Elbehos Street, Dokki, Cairo, Egypt;
e-mail: manal_elshmaa@hotmail.com

tological and inflammatory disorders were excluded. Their underlying renal disorders were reflux nephropathy (n = 1 [3.33 %]), glomerular disease (n = 5 [16.67 %]), hereditary causes (n = 6 [20 %]), anatomic causes (n = 9 [30 %]) and unknown causes (n = 9 [30 %]).

All patients received recombinant human erythropoietin (rHu-EPO) at a dose of 500–12000 IU/week. Twenty healthy subjects (average age 10 ± 1.07 years [range 3–17 years], 10 [50 %] male, 10 [50 %] female) were recruited as controls (NS). For all patients and controls included in this study, informed consent was given by their respective parents.

All patients were subjected to

- compilation of an extensive medical history
- thorough clinical examination
- measurement of hemodialysis adequacy: the delivered dose of HD was described as the fractional clearance of urea as a function of its distribution volume (Kt/V) and was determined using the Kt/V natural logarithm formula [18]
- complete blood count
- pre- and post-dialysis kidney function test
- serum albumin estimation
- estimation of plasma concentration of uric acid and cholesterol by standard laboratory methods using AU400 Olympus
- assay of total antioxidant capacity using colorimetric assay
- assay of MDA by spectrophotometry
- assay of hs-CRP by chemiluniscent immunometric assay
- blood sample collection: serum from all HD patients was obtained by collecting 5 ml whole blood prior to dialysis and by immediate centrifugation for 10 min at 5000 rpm at 4 °C. The centrifuged serum was transferred into sterile tubes. All samples were stored at –70 °C until the assay
- determination of total antioxidant capacity: TAC were determined colorimetrically by an enzymatic reaction which involves the conversion of 3, 5, dichloro-2-hydroxy benzene sulphonate to a colored product [19]
- determination of malondialdehyde (MDA) in serum: this assay is based on the reaction of carbonyl complexes that can be measured spectrophotometrically according to the method of Draper and Hadley [20]
- determination of high-sensitivity CRP in serum: Immulite/Immulite 1000 is a solid-phase chemiluminescent immunometric assay (supplied by Siemens Medical Solution Diagnostics) [21].

Statistical Analysis

SPSS (Statistical Package for Social Sciences) version 11.0 was used in data analysis. Data were summarized as mean ± standard deviation, range and percentage. Student's t test for quantitative independent variables was used for analysis of the difference between two groups. To predict the associations between TAC, MDA and CRP the Pearson and Spearman Rho correlation analysis was performed as well as other numerical variables. Multiple linear regression analysis was performed to determine the contribution of various factors as independents or covariates to TAC, MDA or CRP as the dependent variables. P value was significant at a 0.05 level.

Results

Demographic and clinical data of the studied groups are shown in Table 1. There was no significant difference in age and gender between HD patients and controls.

Table 2 shows the hematological data and the biochemical profile of patients and healthy individuals. The concentration of antioxidant uric acid and creatinine in HD patients were significantly increased compared to NC. Also, there was a significant statistical difference between HD patients and NC as regards cholesterol concentration.

Table 1. Demographic and clinical data of the studied groups

Parameters	HD patients	Controls	p
No of subjects	30	20	
Gender (♂/♀)	17/13 (56.67 %/43.33 %)	10/10 (50 %/50 %)	ns
Age (yrs)	10.53 ± 3.43	10 ± 7.07	ns
Hemodialysis (yrs)	2.82 ± 1.37		
Equilibrated Kt/V	1.90 ± 0.33		
Nephropathies			
Anatomic	9 (30 %)		
Hereditary	6 (20 %)		
Glomerular	5 (16.67 %)		
Reflux nephropathy	1 (3.33 %)		
Unknown	9 (30 %)		
Drugs			
Erythropoietin	30 (100 %)		

Data are means ± SD or number (%) or range as applicable. Significance was estimated using one sample t-test, $p < 0.05$ was considered significant.
Kt/V = adequacy of dialysis; ns = not significant.

Table 2. Hematological data and biochemical profile of the studied groups

Parameters	HD patients	Controls
Hb (g/dl)	10.53 ± 1.83*	14.20 ± 1.50
Creatinine (mg/dl)	6.17 ± 1.45*	0.78 ± 0.35
Predialysis urea (mg/dl)	65.92 ± 14.91*	7.80 ± 2.64
Uric acid (mg/dl)	6.36 ± 1.48*	2.77 ± 1.34
Cholesterol (mg/dl)	191.90 ± 50.71*	145 ± 37.06
Albumin (g/dl)	3.67 ± 0.35**	4.92 ± 0.39

Data are reported as means ± SD
* p was significant if < 0.001 ; ** p < 0.01; Hb = hemoglobin

Plasma concentration of TAC measured in renal patients on HD was significantly higher (2.24 ± 0.64 μmol/l) than in NC (0.16 ± 0.07 μmol/l), $p < 0.001$. The concentration of the lipid peroxidation product, MDA, in the serum of HD patients was significantly increased (2.05 ± 0.39 μmol/l) compared to NC (1.01 ± 0.41 μmol/l), $p < 0.001$ (Fig. 1).

Figure 2 shows a comparison between the value of hs-CRP in the sera of HD patients and control subjects. The hs-CRP values were higher in HD patients (6.57 ± 5.57 mg/l) than in NC (0.19 ± 0.03 mg/l), $p < 0.001$. Raised hs-CRP concentration (> 10 mg/l) was found in 30 % of HD patients. Patients with levels of hs-CRP > 10 mg/l did not show significant differences in TAC and MDA concentration from those who had hs-CRP levels within normal range.

Positive correlations were observed between hs-CRP and both TAC concentrations and MDA levels in the serum of HD patients ($r = 0.52$, $p < 0.08$; $r = 0.75$, $p < 0.04$, respectively) (Tab. 3). No correlation was found between hs-CRP and TAC concentrations or hs-CRP and MDA levels in the serum of NC.

Table 4 shows the correlations of markers of oxidative stress and hs-CRP with individual variables in HD patients. The TAC concentrations were positively correlated with uric acid levels ($r = 0.66$, $p < 0.002$) as well as predialysis urea ($r = 0.35$, $p < 0.08$). The hs-CRP value was inversely corre-

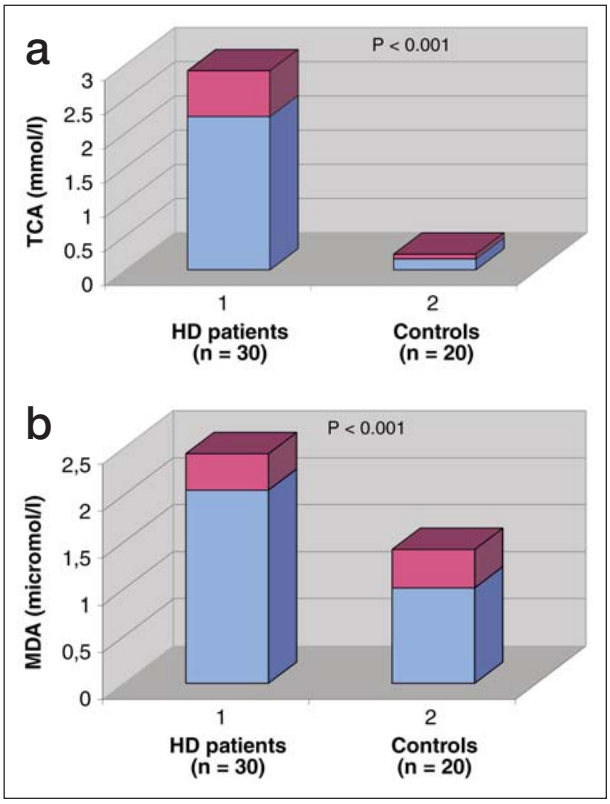

Figure 1. Serum total antioxidant capacity (TAC) **(a)** and malondialdehyde (MDA) **(b)** levels in hemodialyzed patients (HD) and in normal individuals. Columns represent mean ± SD.

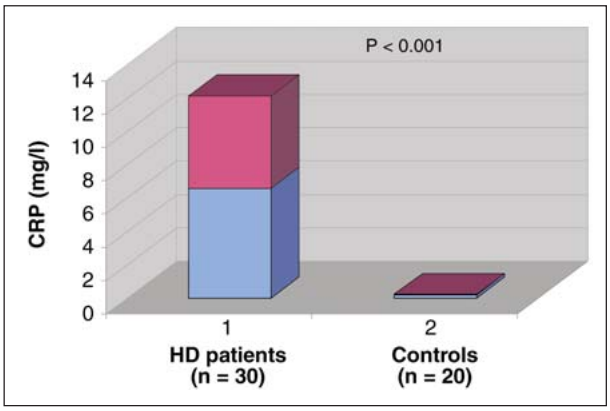

Figure 2. Serum CRP levels in hemodialyzed patients (HD) and in normal individuals. Columns represent mean ± SD.

lated with cholesterol concentration in the serum of HD patients ($r = –0.35$, $p < 0.03$). Inverse correlation was found between serum MDA concentration and Hb in blood of HD patients ($r = –0.42$, $p < 0.01$).

Table 5 on correlating the hs-CRP values to the markers of oxidative stress and other individual variables by multiple linear regression analysis, TAC concentration, MDA levels, cholesterol concentration, Hb and equilibrated Kt/V were variables that are independently associated with elevated hs-CRP values ($p < 0.05$).

TAC concentration was independently associated with the hs-CRP level, cholesterol concentration and Hb level in HD patients, while the MDA level was independently associated with TAC concentration, Hb value, and albumin concentration.

Table 3. Correlation between markers of oxidative stress and hs-C-reactive protein in hemodialyzed patients

Parameter	TAC		MDA	
	r	p	r	p
hs-CRP	0.52	0.08*	0.75	0.04*

Correlation was performed by Pearson's analysis.
* Significant $p < 0.05$.
TAC = total antioxidant capacity; MDA = malondialdehyde; hs-CRP = high-sensitivity C-reactive protein

Table 4. Correlation of oxidative stress markers and hs-CRP with individual variables in hemodialyzed patients

Parameters	TAC		MDA		hs-CRP	
	r	p	r	p	r	p
Age	0.03	ns	0.07	ns	0.12	ns
HDD	0.07	ns	0.01	ns	0.04	ns
KT/V	0.28	ns	0.07	ns	0.13	ns
Hb %	0.25	ns	–0.42	0.01*	0.17	ns
Creatinine	0.31	ns	0.06	ns	0.01	ns
Predialysis urea	0.35	0.08[a]*	0.24	ns	0.03	ns
Uric acid	0.66	0.002[a]*	0.08	ns	0.03	ns
Cholesterol	0.21	ns	0.23	ns	0.35	0.03[b]*
Albumin	0.14	ns	0.32	ns	0.24	ns

Correlation was performed by [a] Pearson's or [b] Spearman Rho analysis.
* Significant $p < 0.01$; HDD = hemodialysis duration; Hb = hemoglobin

Table 5. Multiple linear regression analysis comparing the correlation of hs-C-reactive protein level and markers of oxidative with individual variables in stress serum of hemodialysis patients

Variables	β	p
Dependent variables, hs-CRP		
TAC	0.51	0.08*
MDA	0.49	0.08*
Cholesterol	–0.48	0.06*
Hb	–0.49	0.07*
Kt/V	–0.72	0.01*
Dependent variables, TAC		
hs-CRP	0.35	0.02*
Cholesterol	0.73	0.001*
Hb	0.42	0.01*
Dependent variables, MDA		
TAC	0.51	0.03*
Albumin	0.42	0.07*
Hb	–0.35	ns

* $p < 0.05$ was considered significant
TAC = total antioxidant capacity; MDA=malondialdehyde; Hb = hemoglobin; HDD = hemodialysis duration

Discussion

Chronic uremia is considered a proinflammatory state associated with high cardiovascular morbidity and mortality [22]. Patients treated by renal replacement therapy are subjected to a wide range of biochemical disorders, some of which are ascribed to increased oxidative stress [3, 4, 8, 14]. Our finding that the TAC concentration was elevated in HD patients was consistent with this fact. There is currently great interest in the assessment of the antioxidant status, as antioxidant deple-

tion may contribute to a number of diseases. Several methods reported in recent years give a single measure of the total antioxidant capacity of plasma, and it has been suggested that this may represent a useful way of predicting the risk of free radical-induced tissue damage [23]. Methods of measuring the total antioxidant capacity are attractive in several ways: a small sample volume is required, the interactions between individual antioxidants are accounted for, and the effects of unknown antioxidants are also taken into account [24]. This finding is in agreement with Samouilidou et al [25] who reported an increased level of TAC concentration in patients on peritoneal dialysis (PD) and in HD patients. Also, Jackson et al [26] found that the total antioxidant capacity level in the serum is increased in HD patients who are susceptible to oxidative stress.

In the present study, there was an increased concentration of malondialdehyde in dialysis patients as compared to NC, suggesting increased lipid peroxidation and that a large amount of adehydic products is formed [25]. This finding is in keeping with most previously published findings, as Samouilidou and Grapsa [27] found that before HD, TAC and MDA levels were higher than those in the NC, after HD, these levels decreased significantly but were higher than in NC.

In this study, hs-CRP levels were increased in HD patients as compared to NC, and it is thought that this may be an independent risk factor that may cause progressive atherosclerosis [13, 16, 17]. As is known, one of the mechanisms that may account for increased oxidative stress in dialysis is chronic inflammation. The release of proinflammatory cytokines such as interleukin 1 (IL-1), IL-6 and tumor necrosis factor during a dialysis session is considered a reason for elevated plasma CRP levels [28].

It has been shown that hs-CRP > 50 mg/l is strongly suggestive of an inflammatory process, while a level < 10 mg/l may exclude it [15, 16]. The present study showed that the percentage of patients with hs-CRP > 10 mg/l was 30 %. This is in agreement with a previous study [13], where it was assumed that HD patients are characterized by a higher inflammatory activity that may probably result in a chronic state of acute phase response. The high inflammatory activity in HD patients is attributed to the activation of complement components by bioincompatible dialyzer membranes [28, 29]. In the literature, a wide range of hs-CRP levels in CRF patients is reported. Zimmermann et al [17] reported that the increase in hs-CRP levels > 10 mg/l was 46 % in HD patients. Owen and Lowrie [30] reported that this increase was 35 %.

The present study showed a positive correlation between the hs-CRP level and TAC concentration. Different inflammatory activity of HD patients may be responsible for this correlation [24]. hs-CRP levels were proven to be correlated with the levels of specific components of antioxidant defense system such as α-tocopherol (expressed in lipid normalized values) [7]. This is in agreement with Nguyen-Khoa et al [7] who found a positive correlation between the hs-CRP level as a marker of inflammation and total antioxidant status in patients treated by renal replacement therapy.

It is also of interest to note that the hs-CRP concentration was correlated positively with MDA in our study. Donica [10] reported that the CRP level has been shown to be associated with another product of lipid peroxidation, the esterified F2-isoprostanes. This might be suggestive of a possible selective stimulation of CRP release by peroxyl radicals produced by oxidized lipids under conditions of oxidative stress.

Our study showed a positive correlation between TAC concentration and uric acid level in HD patients. This result is in accordance with the result of Jackson et al [26] who found that serum urate was increased as was expected, given the key role of the kidney in the elimination of urate from the body. Total antioxidant content was increased almost entirely due to increased urate. Our results highlight one pitfall of measuring total antioxidant capacity: changes in one of the major contributors (in this case, urate) may mask potentially important changes in other antioxidants; we would have concluded that the chain-breaking antioxidant capacity was increased in dialysis patients. Urate is an efficient antioxidant in some settings, particularly against ozone-derived radicals. However, it is not a good scavenger of some biologically important radical species, and increased urate concentrations are unlikely to provide an adequate antioxidant defense in the presence of deficiencies of other antioxidant systems [31, 32]. We therefore believe that it is important to measure the major chain-breaking antioxidants individually in addition to total antioxidant capacity.

This study showed an inverse correlation between MDA serum concentration and hemoglobin in the blood of HD patients. Lucchi et al [33] found an inverse correlation between the lipid peroxidation product and hemoglobin in the blood of HD patients and the highest correlation was achieved for a second-order regression – this might indicate two or more different mechanisms leading to the dependence shown. Besides the effect of reduced RBC survival due to uremia [34], the accelerated LPO at the low Hb level might be explained by oxidative stress due to the anemic condition itself. Anemic patients showed an increased frequency of ventilation at peak-exercise because of the limited oxygen transport capacity, implying anaerobic metabolism due to hypoxemia and ischemia [35]. There are important radical sources that may be responsible for oxidative stress in anemic HD patients: final purine degradation via xanthine oxidase reoxygenation of the temporarily hypoxic tissue, activation of the polymorphonuclear lymphocyte and partial uncoupling of oxidative phosphorylation [36, 37]. On the other hand, since RBC deficiency accompanies a deficit of enzymes able to metabolize aldehydic LPO products, the blood of uremic patients loses a major part of its antioxidant power [38].

Our study showed an inverse correlation between the hs-CRP level and cholesterol concentration in patients on HD. This result may be due to a malnutrition-inflammation complex common in patients undergoing HD [25]. A possible mechanism might include increased uptake of cholesterol by oxidized macrophage via an oxidized cholesterol receptor. Observed in vitro, this effect might be attributable to an increased number of cholesterol receptors on the surface of oxidized macrophages [39]. This result is in agreement with the results of Samouilidou et al [25] who found that the hs-CRP levels were proven to be negatively correlated with the level of total cholesterol in HD patients as cholesterol is one of the antioxidants increased in the serum of patients on HD and has a role in the exacerbation of oxidative damage and the generation of atherosclerosis.

The present study on correlating the serum hs-CRP level to markers of oxidative stress and to different individual variables by multiple linear regression analysis revealed the independent associations between the hs-CRP level in the serum of HD patients and TAC concentration, MDA value, cholesterol concentration, Hb concentration and adequacy of dialysis as measured by equilibrated Kt/V. These associations revealed that lipid peroxidation may be involved in the occurrence of a microinflammation state. The complex interaction between oxidative stress and microinflammation may result in the accelerated atherosclerosis seen in CRF [1].

We also found TAC independently associated with the hs-CRP level, cholesterol concentration and hemoglobin in HD patients and this result confirms the relation between

oxidative stress and the cardiovascular risk factors in the form of hs-CRP and cholesterol levels [2].

In this study, the MDA level was independently associated with the TAC concentration, hemoglobin value and albumin concentration which is a parameter of the nutritional status. MDA accumulation represents a cardiovascular risk factor statistically correlated with TAC and this indicates that susceptibility to oxidative stress is strongly related to the levels of MDA produced in the serum [3]. Carluccio et al [40] reported that MDA is independently associated wit nutrition and energy status in patients with chronic renal failure. Lucchi et al [33] reported that the close association of the MDA level with Hb concentration reveals that a substantial part of the oxidative stress is due to renal anemia.

Conclusion

Our data show that in spite of increased antioxidant capacity in HD patients there is an increased susceptibility to oxidative stress strongly related to the levels of MDA produced in the serum. The hs-CRP level is higher in HD patients than in NC and this is indicative of a higher degree of inflammatory activity in these patients. A synergism between oxidative stress and inflammation in HD patients may result in accelerated atherosclerosis seen in these patients. A substantial part of the oxidative stress is due to renal anemia.

Recommendations

- The identification of MDA as a predictor of CVD in HD patients may underscore the role of oxidative stress as a cardiac risk factor in this patient population, whether exacerbated by dialysis itself or contributed to by some factor in uremic plasma or because of the alteration in the efficiency of antioxidants.
- A prospective study or, alternatively, a clinical trial in which antioxidants could be used to reduce oxidative stress in this group is required. Supplementation with vitamin E may be a promising antioxidant intervention in these patients.
- Further investigation on various mechanisms of increased oxidative stress induced by CRP elevation in dialysis patients would enlighten the possible pathways that lead to the exacerbation of oxidative damage and the generation of atherosclerosis.

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