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Original Article

The Relationship between the Antioxidant System, Oxidative Stress and Dialysis-Related Amyloidosis in Hemodialysis Patients

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ABSTRACT. End-stage renal disease (ESRD) is associated with several complications that are partly due to excess amounts of reactive oxygen species and/or decreased antioxidant activity. Dialysis-related amyloidosis (DRA) has also been linked to increased oxidative stress. The aim of this study was to investigate the relationships between the antioxidant system, including superoxide dismutase (SOD), malonyldialdehyde (MDA), various biochemical parameters and shoulder amyloidosis, in hemodialysis patients. We studied 107 non-diabetic chronic dialysis patients. The SOD levels correlated with right and left biceps tendon thickness (r = -0.219, *P* = 0.048 and r = -0.236, *P* = 0.031, respectively), MDA (r = -0.429, *P* = 0.000) and albumin levels (r = -0.319, *P* = 0.001). MDA levels correlated with right and left biceps thickness (r = 0.291, *P* = 0.006 and r = 0.337, *P* = 0.001, respectively) and β_2 microglobulin levels (r = 0.455, *P* = 0.000). We also identified the statistically significant relationships between MDA levels and supraspinatus tendon thickening (greater than 7 mm) and right and left biceps tendon thickness (*P* = 0.022, *P* = 0.040 and *P* = 0.005, respectively). Our data suggest the complex relationship between antioxidants and oxidative stress and further support the roles of oxidative stress and antioxidants in DRA.

Introduction

Uremia is described as an increased oxidative stress state due to an imbalance between the generation of oxidant compounds and insufficient antioxidant defense mechanisms, and may result in increased tissue damage.[1-6]

Because free radicals have very short half-lives, measurement of different stable oxidized compounds, such as lipid peroxidation, advanced glycation, oxidation lipid, protein products, nucleic acid oxidation derivatives and enzymatic antioxidants, including superoxide dismutase (SOD), catalase and glutathione peroxidise (GPx),[2,7] are used to clinically assess oxidative stress.

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End-stage renal disease (ESRD) is associated with many complications that result from excess amounts of reactive oxygen species and/or decreased antioxidant activity. Hemodialysis (HD) patients are exposed to both oxidative stress and inflammation, and both are closely related cellular processes.[2,8] Growing evidence from experimental and clinical studies has implicated oxidative stress in the pathogenesis of atherosclerosis and other complications of ESRD, including dialysis-related amyloidosis.[2,9]

β_2 microglobulin (β_2M) is a low molecular weight protein (11,800 Da) that is produced by all cells expressing the major histocompatibility complex class I. β_2M is recognized as a surrogate marker of middle-molecule uremic toxins and is a key component in the pathogenesis of dialysis-associated amyloidosis.[10-12] β_2M amyloid fibrils primarily accumulate in the osteoarticular tissues, causing musculoskeletal symptoms, including polyarthralgia and bone cysts.[13,14]

Ultrasonography has been used to successfully diagnose dialysis-related amyloidosis in the shoulders of long-term HD patients. Sonographic findings associated with amyloidosis of the shoulder include thickening of the rotator cuff (i.e., supraspinatus tendon, the synovial sheath of the long head of the biceps tendon and the subacromial - subdeltoid bursa) and the presence of nodules within or around the shoulder joint.[15-17]

The aim of our study was to determine the relationship between serum β_2M, SOD and MDA together with various biochemical parameters and shoulder amyloidosis in HD patients.

Materials and Methods

We studied 107 non-diabetic chronic HD patients at the Kütahya State Hospital's dialysis unit and a private dialysis center. At the time of our study, all patients were receiving bicarbonate-buffered dialysis therapy three times per week for 4 h. For all patients, dialysis therapy was initiated after their creatinine clearance had fallen below 8 - 15 mL/min and/or pharmacological treatment and diet had proven inadequate in controlling their clinical symptoms.

Patients were excluded from participating in the present study if they had an episode of acute infection in the 3 months preceding enrollment to the study, neoplasm, severe malnutrition or severe hypoalbuminemia (<2.9 g/dL), liver cirrhosis or clinically symptomatic cardiac or vascular disease. Patients were also excluded if they were heavy smokers (defined as smoking >20 cigarettes/day for 1 year prior to their recruitment).

This study was performed in accordance with the Declaration of Helsinki and with the approval of the local ethics committee. Informed written consent was obtained from all patients prior to their entry in the study.

For all patients, dialysis was carried out using a Fresenius 4008 B HD machine (Fresenius Medical Care, Germany) and either synthetic or semi-synthetic standard (low-flux) membranes. The water used for dialysis was purified using a reverse osmosis treatment system equipped with an endotoxin filter (Aqua RO modular; Fresenius Medical Care). The quality of the dialysis water was checked regularly according to the recommended guidelines. During HD treatment, patient blood flow rate and dialysate flow rate were maintained at 250 - 350 mL/min and 500 mL/min, respectively. The patients included in our study had vascular access for HD through arteriovenous fistulas located in their upper extremities or permanent catheters. The adequacy of dialysis (as measured by Kt/V) was calculated using the single-compartment Daugirdas formula, standard urea removal ratio [URR = 100 (1 – R), where R = post-dialysis urea/pre-dialysis urea] and normalized protein catabolic rate (nPCR, g/kg/day) using the formula recommended by the DOQI HD Adequacy Work Group,[18,19]

Peripheral venous blood samples were collected from HD patients just prior to the start of a midweek dialysis session. Serum glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, albumin, calcium, phosphorus, iron and iron-binding capacity (IBC) were

measured using a Roche Integra 400 Autoanalyzer (Roche, USA). Complete blood count measurements, including hemoglobin (Hb), hematocrit (Hct) and lymphocyte, were performed using a Beckman Coulter HMX Autoanalyzer (Beckman Coulter, USA). Intact parathyroid hormone (PTH) was measured using electrochemiluminescence (Roche E170) and anti-hepatitis C virus levels were assessed using immunoenzymatic assays (RADIM ALISEI, Italy). C-reactive protein (CRP) was assayed on a Roche Integra 400 using an immunoturbidimetric method. Low-density lipoprotein cholesterol (LDL-chol) concentrations were calculated using Friedewald's formula.[20]

Ten milliliters of blood was collected from the cubital veins of all subjects in EDTA, heparin and non-gel serum tubes. After coagulating the blood specimens, they were centrifuged at ≤1300 RCF for 10 min to separate the serum. All assays were performed in the biochemistry laboratories of the Selcuk University, Meram Education and Research Hospital, Faculty of Medicine.

SOD and MDA levels were determined in red blood cells and serum samples collected from HD patients. Erythrocyte SOD activity was determined using the McCord and Ransel's method.[21] The activity of this enzyme was expressed as U/gr hemoglobin. MDA levels were assayed using a thiobarbituric acid method developed by Draper and Hadley.[22]

We used ultrasonography to evaluate the supraspinatus and biceps tendon thickness, supraspinatus and biceps tendon tears, synovial thickening and the presence of hypoechoic deposits around the tendons and within the subdeltoid bursae and biceps tendon sheath and the presence of fluid within the subdeltoid bursae and biceps tendon sheath. Consistent with previously published cut-off values, supraspinatus and biceps tendon thickening greater than 7 and 4 mm, respectively, were considered to be indicative of abnormal thickening.[17,23-26]

Bilateral shoulder sonograms were performed on all patients included in our study. Maximal thickness of the supra spinatus tendon was measured on a longitudinal view in front of the lateral part of the humeral head.

All sonograms were performed by a single ultrasonographer using an Acuson Antares ultrasound system (Siemens, Germany) with a high-frequency (5 or 7.5 Mega Hertz) linear-array transducer.

Statistical Analysis

Clinical and laboratory data are expressed as means ± standard deviation (SD). Differences in the means between our dichotomized patient groups were evaluated using unpaired Student's *t*-tests. Data that showed skewed distributions were compared using the Mann - Whitney *U*-test. Chi-square tests were used to compare categorical data between the groups. Correlations were evaluated using Pearson's correlation tests. *P*-values <0.05 were considered statistically significant. All data were analyzed using SPSS 12.0 for Windows software (SPSS Inc., Chicago, IL, USA).

Results

Of the 107 studied patients, 56% were female and 21.5% tested positive for hepatitis C virus (HCV). Demographic, clinical and biochemical characteristics of the study patients are presented in Tables 1 and 2. Forty-seven (43.9%) patients had no shoulder involvement. Of the 60 studied patients with symptomatic shoulders, 49 (80.1%) had involvement in both shoulders.

Fifty-five (51.4%) of all the studied shoulders had non-homogeneous thickening (7 mm) of the supraspinatus tendon, 44 (41.1%) had abnormal thickening (≥4 mm) of the biceps tendon and 19 (17.8%) had hypoechoic deposits in the biceps tendon sheath. Thirty-seven (34.6%) had hypoechoic deposits in the subdeltoid bursae. Supraspinatus tendon and biceps tendon tears were seen in 28 (26.2%) and three (2.8%) shoulders, respectively.

β_2M levels correlated with age (r = 0.248, *P* = 0.014), dialysis duration (r = -0.516, *P* = 0.000), residual urine (r = 0.263, *P* = 0.010) and total protein levels (r = -0.240, *P* = 0.017).

SOD levels correlated with right biceps tendon

Table 1. Demographic and clinical characteristics of the study patients.

	Mean	Minimum	Maximum
Age	57.1 ± 12.8	26	85
Duration of dialysis	72.4 ± 53.9	12	281
Residual urine	359 ± 633	0	4900
Kt/V	1.4 ± 0.1	0.8	1.7
n PCR	0.9 ± 0.2	0.7	1.3
URR	71.0 ± 6.0	46.4	83.9
Right supraspinatus thickness	7.1 ± 1.5	4.0	13.0
Left supraspinatus thickness	6.9 ± 1.5	2.8	12.0
Right biceps thickness (mm)	4.0 ± 1.6	2	14
Left biceps thickness (mm)	3.9 ± 1.3	2.0	8.3

Kt/V: Clearance.time/volume, nPCR: Normalized protein catabolic rate, URR: Urea reduction rate.

Table 2. Biochemical parameters of the study patients.

	Mean	Minimum	Maximum
β_2M (mg/L)	17.8 ± 5.00	5.00	26.8
SOD (U/g Hb)	309 ± 52.8	185	428
MDA (µmol/L)	10.0 ± 6.9	2.7	29.4
CRP (mg/L)	132 ± 17.9	0.27	81.6
Ferritin (ng/mL)	830 ± 552	82	1900
PTH (pg/mL)	477 ± 302	28	1617
Calcium (mg/dL)	8.6 ± 0.8	6.2	10.2

ng: Nanogram, pg: Picogram

thickness (r = -0.219, *P* = 0.048), left biceps tendon thickness (r = -0.236, *P* = 0.031), MDA (r = -0.429, *P* = 0.000) (Figure 1), PTH (r = -0.256, *P* = 0.015), BUN (r = -0.215, *P* = 0.026), creatinine (r = -0.236, *P* = 0.014), albumin (r = -0.319, *P* = 0.001) and total protein levels (r = -0.207, *P* = 0.038).

MDA levels correlated with right biceps thickness (r = 0.291, *P* = 0.006), left biceps thickness (r = 0.337, *P* = 0.001), β_2M (r = 0.455, *P* = 0.000) (Figure 2), BUN (r = 0.478, *P* = 0.000) and creatinine levels (0.245, *P* = 0.010).

HCV positivity was related to dialysis duration (*P* = 0.000), SOD (*P* = 0.006), β_2M levels (*P* = 0.029), presence of biceps tendon thickening (>4 mm) (*P* = 0.002), right biceps tendon thickness (*P* = 0.032), left biceps tendon thickness (*P* = 0.005) and fluid within the biceps sheaths (*P* = 0.0349).

When patients were dichotomized into two groups based on the mean values of the patients (the mean values of the MDA and β_2M were 10 µmol/L and 17.8 mg/L, respectively), our analysis identified a statistically significant

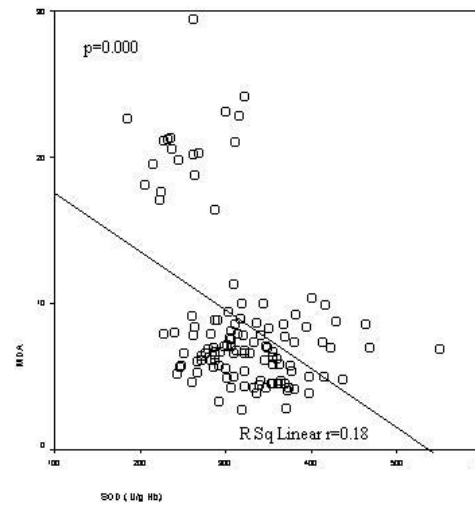

Figure 1. The negative correlation between SOD and MDA levels.

relationship between β_2M levels and the presence of supraspinatus tendon thickening (>7 mm), abnormal biceps tendon thickening (>4 mm) and hypoechoic deposits around the tendons and within the subdeltoid bursae and biceps sheaths (*P* = 0.030, *P* = 0.003, *P* = 0.015

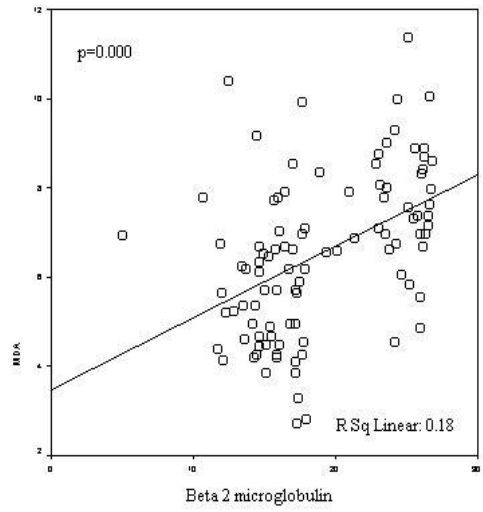

Figure 2. The correlation between MDA and beta- 2 microglobulin levels.

and P = 0.004, respectively). We observed a significant relationship between MDA levels and residual urine (P = 0.035). Residual urine levels were lower in patients with high MDA levels than in those with low MDA levels (193.9 ± 319.5 vs. 437.3 ± 685.1 mL/24 h). We identified statistically significant relationships between MDA levels and shoulder involvement (P = 0.019) and between MDA levels and supraspinatus tendon thickening >7 mm (P = 0.022). The proportion of patients with supraspinatus tendon thickening >7 mm among those with high MDA levels was higher compared with those with low MDA levels (59% vs. 41% of patients with supraspinatus tendon thickening >7 mm). Similarly, we observed a statistically significant relationship between MDA levels and left and right biceps tendon thickening (P = 0.005 and P = 0.040, respectively). Biceps tendon thickness was higher in patients with high MDA levels than in those with low MDA levels (4.4 ± 1.3 mm vs. 3.7 ± 1.1 mm for left biceps tendon thickness and 3.8 ± 1.4 mm vs. 4.3 ± 1.2 mm for right biceps tendon thickness). Levels of β_2M and BUN were higher in patients with high MDA levels compared with those with low MDA levels (P = 0.000, P = 0.003 and P = 0.019, respectively).

Discussion

β_2M amyloidosis is a major long-term complication of dialysis treatment. Previous studies have shown that inflammation status, low albumin levels and residual glomerular filtration rate of uremic patients were predictive of β_2M amyloidosis lesions, suggesting that the pathogenesis of β_2M amyloidosis is multifactorial.[27] In the present cross-sectional study, we investigated the relationship between SOD, MDA, various biochemical parameters and dialysis-related amyloidosis in HD patients.

There is a delicate equilibrium between the antioxidant defense system and the free radical homeostasis in humans. Perturbation of this balance, referred to as oxidative stress, induces cellular damage. Oxidative stress plays a significant role in the development of inflammation in dialysis patients and contributes to atherosclerosis, various inflammatory conditions (e.g., β_2M amyloidosis), certain cancers and the aging process.[2,28-33]

The natural antioxidant system consists of enzymes and compounds that protect against reactive oxygen species-mediated cytotoxicity and tissue damage.[2,7,28,34,35] Previous investigations regarding the antioxidant enzymes that participate in free radical scavenging have yielded controversial results. Increased erythrocyte SOD and CAT activities in adult patients with ESRD are thought to be adaptive mechanisms of oxidative stress.[7,30] Several other studies have shown, however, that antioxidant enzyme activities are significantly reduced in ESRD patients.[36-41] Ece et al[7] reported that children with ESRD had significantly increased MDA concentrations and decreased SOD, CAT and GPx levels compared with the controls.

In our study, SOD negatively correlated with MDA levels. MDA levels positively correlated with β_2M, BUN and creatinine levels and negatively correlated with SOD. In our group comparisons, the levels of β_2M and BUN were higher in patients with higher levels of MDA compared with those with lower levels of MDA. We identified a significant relationship between MDA levels and residual urine. Resi-

dual urine was lower in patients with high MDA levels compared with patients with low MDA levels. The negative correlations observed between MDA and SOD levels can be attributed to the increased oxidative stress. Further, we speculate that these decreased enzyme activities may be due to several factors, including consumption during free radical production, exposure to uremic toxins and deficiencies of trace elements (i.e., Zn, Se and Cu).

Fry et al[42] reported that serum β_2M concentrations increase as the duration of HD increases. However, after 5 - 10 years of dialysis therapy, the β_2M levels plateau and, after 18 years, these levels have been shown to decrease.[43,44] Several studies have suggested that the presence of inflammation and the duration of dialysis are the most important determinants of oxidative stress in HD patients.[45,46] Likewise, the duration of dialytic therapy and patient age at the beginning of HD are critical factors associated with the development of DRA. DRA is often observed within 3 - 5 years of the initiation of dialysis.[17,47] Cianciolo at al[27] found that inflammation, low albumin, low Hb, age and residual GFR of uremic patients are all predictive of β_2M lesions. In our study, β_2M correlated with age, dialysis duration, residual urine, MDA and total protein levels. We also identified a statistically significant relationship between the levels of β_2M and supraspinatus tendon thickening, biceps tendon thickening and hypoechoic deposits around the tendons and within the subdeltoid bursae and biceps tendon sheath.

DRA has previously been linked to increased oxidative stress. Several studies have reported increased markers of protein oxidation such as advanced oxidation protein products and lipid peroxidation (thiobarbituric acid-reactive substances, MDA, 4-hydroxynonenal, oxidated LDL and esterified F2 isoprostanes) as well as of oxidation of carbohydrates and nucleic acids in uremic patients.[2,13,14,39] In our study, we identified a significant relationship between MDA levels and shoulder involvement. There is a statistically significant relationship between MDA levels and supraspinatus tendon thickening. The proportion of patients with supraspinatus tendon thickening >7 mm among those with high MDA levels was higher compared with those with low MDA levels. Furthermore, biceps tendon thickness was higher in patients with high MDA levels than in those with low MDA levels. SOD levels were negatively correlated with biceps tendon thickness. Our results clearly display the complex interactions between the antioxidant system, MDA (a systemic oxidative stress marker) and shoulder involvement due to DRA.

HCV positivity related to dialysis vintage, SOD, β_2M levels, presence of biceps tendon thickening (>4 mm), right biceps tendon thickness, left biceps tendon thickness and fluid within the biceps sheaths. Based on our results, we hypothesize that HCV positivity may contribute to the formation of DRA by increasing the systemic oxidative stress.

The limitations of our study included the use of ultrasonography to diagnose the DRA. Although scintigraphy using radio-labeled β_2M is much more sensitive, we could not perform the scintigraphy using radio-labeled β_2M for technical reasons. Furthermore, for ethical reasons, we did not systematically biopsy the shoulders of our HD patients. As shown by Jadoul et al,[25] sonographic and histological evidence of amyloid deposits have similar sensitivity to effectively detect β_2M amyloid deposits.

In conclusion, our study suggests the complex relationship between oxidative stress, antioxidants and DRA. Additional studies are needed to verify this connection between them.

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