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Correlation of anti-heat shock protein 70 antibodies serum level with malnutrition–inflammation score in hemodialysis patients

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Abstract

Background Increased levels of circulating heat shock protein 70 antibodies (anti-Hsp70) have been reported in hemodialysis (HD) patients. Since the anti-Hsp70 correlates with inflammation, it may associate with the malnutrition–inflammation score (MIS). The aim of this study was to determine whether the increased MIS score in HD patients are related to circulating levels of anti-Hsp70.

Method Ninety HD patients with an arteriovenous fistula, aged 30–65 years, who underwent three hemodialysis sessions a week for at least the past 3 months at a hemodialysis center were enrolled in this cross-sectional study. Patients were divided based on MIS score to two groups, and the clinical and biochemical variables were compared between them. MIS cutoff score of ≥ 5 indicated the presence of malnutrition. The association between categorized MIS and anti-Hsp70 was examined using regression models adjusted for diabetes mellitus, hemodialysis vintage, BMI, albumin, hs-CRP, IL6 and endotoxin levels as confounding factors.

Results The univariate regression analysis revealed a significant association between MIS ≥ 5 and hemodialysis vintage, uric acid, hs-CRP, IL-6, endotoxin and serum anti-Hsp70 level. After adjusting the confounders, the association between MIS ≥ 5 and serum anti-Hsp70 level remained significant.

Conclusion These data support the role of serum anti-Hsp70 in the development of malnutrition in HD patients. However, further studies with body composition assessments and better generalizability are required to investigate the association between nutritional status and circulating anti-Hsp70 level in HD patients.

Keywords Malnutrition–inflammation score · MIS · Heat shock protein · anti-Hsp70 · Hemodialysis

Introduction

The presence of chronic inflammation and protein–energy wasting (PEW) syndrome, also known as Malnutrition–inflammation complex syndrome (MICS), a condition characterized by metabolic and nutritional changes leading to depleted stores of protein and energy, has been considered as one of the strongest indicators of death in hemodialysis (HD) patients [1]. Malnutrition, persistent inflammation, and atherosclerosis syndrome lead to PEW by several mechanisms including stimulation of both direct and indirect mechanisms of muscle proteolysis [2]. In HD patients, various studies reported that the prevalence of PEW varies between 15 and 76%, according to the type of dialysis modality, nutritional assessment tools, and origin of the patient population [3]. The severity of PEW/MICS can be evaluated using a semi-quantitative tool, the malnutrition–inflammation score (MIS), which was previously designed for dialysis patients [4]. The previous studies demonstrated that MIS is a useful and simple instrument, which is associated with increased inflammation and risk of mortality in HD patients [4]. On the other hand, the increased cell death, as a consequence of persistent inflammation, may lead to heat shock proteins (HSP) release in circulation [5]. HSP70 is a family of a larger group of proteins collectively called as heat shock proteins, the expression of which is induced by chemical and physical stress. In general, it seems that intracellular Hsp70 has anti-inflammatory effects,

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while extracellular Hsp70 has pro-inflammatory effects. It is reported that the serum levels of Hsp70 and their antibodies are elevated in HD patients [6, 7]. Various pathophysiologic mechanisms of a higher level of anti-hsp70 level-induced inflammation have been proposed in patients with inflammatory disorders [8–12] and similar pathways may also play role in HD patients with PEW. In addition, PEW contributed to increased catabolism, activation of pro-inflammatory cytokines, and loss of lean body mass [13]; hence, the higher level of serum anti-hsp70 may play a key role in PEW development in HD patients. Therefore, the higher level of serum anti-hsp70 may associate with the MIS score in the pathophysiology of PEW in HD patients. This study investigated the relation between serum anti-hsp70 levels, MIS scores, and PEW in HD patients.

Methods and materials

Participants

In this cross-sectional study, 90 hemodialysis patients were randomly selected from among 216 hemodialysis patients in Emam Khomeini hemodialysis center, Ahvaz, Iran. The inclusion criteria for eligibility were age of 30–65 years, with an arteriovenous fistula and undergoing hemodialysis for at least 3 months before starting the study. Patients with an acute disease, previous kidney transplant or likely to receive a transplant, smoking, medically diagnosed with severe infections, malignancy, chronic liver disease, using a central catheter for hemodialysis access, amputated limbs, hospital admission in recent months, pregnancy and using steroidal and/or nonsteroidal anti-inflammatory drugs, antioxidant, and/or anti-inflammatory supplements within 1 month of study commencement were excluded.

Dialysis duration was 3–4.5 h per session, three times per week, with a blood flow of 250 mL/min and a dialysate flow of 500 mL/min. The patients had a dialysis adequacy as a Kt/V of 1.46 per session in the last 3 months. A researcher was trained to ensure the reliability of the nutritional status assessment and data collection. The MIS measurement was assessed in all of the participants. Blood samples were taken to analyze the biochemical measurements from the patients after an overnight fast. The hemodialysis patients were investigated on a mid-week, before the dialysis session. Clinical and demographic data of the patients were obtained from their hospital records. The other indexes such as age, sex, family history of kidney disease, cause of end-stage renal disease, duration of dialysis, number of dialysis sessions per week, and time of dialysis session were collected through an interview with the patient. The study was in adherence to the Declaration of Helsinki and written, informed consent was obtained from all patients before initiating the study. The Ethics Committee of Ahvaz University of Medical Sciences approved the study protocol (IR.AJUMF.REC.1395.812).

Data collection

Anthropometric measurements

The researcher determined the body weight (kg) and height (cm) measurements after the dialysis session. The height was measured using a stadiometer when the feet were side by side and the head was in the Frankfort plane. Dry weight measurement (with as little clothing as possible) was assessed within 10–20 min after the dialysis session using a Seca scale (Germany) with an accuracy of ± 100 g. BMI values of the patients were calculated with the body weight/height (kg/m^2) equation using body weight and height measurements.

Malnutrition–inflammation score

MIS was computed by a previously suggested method by Kalantar-Zadeh et al. [4]. MIS consisted of four sections (nutritional history, physical examination, BMI and laboratory values) and ten components. The first three sections (nutritional history, physical examination, BMI) include five components adopted from the original subjective global assessment score. The fourth MIS section (laboratory values) includes serum albumin and transferrin levels. Each MIS component has four levels of severity from zero (normal) to three (very severe). The sum of all the ten MIS components ranges from 0 to 30, denoting the increasing degree of severity.

Laboratory methods

Blood samples (7 mL) were drawn immediately before the HD session from each subject in the morning after 12 h of overnight fasting before the midweek dialysis treatment using the slow flow/stop pump technique. The serum was separated (15 min; 3000×*g*; 4 °C) and stored at − 80 °C until analysis. Circulating levels of serum anti-Hsp70 antibodies were assessed using an enzyme-linked immunosorbent assay (ELISA) kit (ab133063; Abcam; USA) with intro- and inter-assay CVs of < 10%. The serum level of IL-6 (CK-E10140; Eastbiopharm; China), hs-CRP (CK-E11183; Eastbiopharma; China) and endotoxins (CK-E10840; Eastbiopharma; China) were measured by using commercially available ELISA kits with intra-assay and inter-assay coefficients of variation of 10% and 12%, respectively. The serum level of uric acid was measured by standard analytical methods (Clauss technique and uricase enzymatic test, respectively; normal range of uric acid levels: 3.4–7 mg/dL for men and

2.4–6 mg/dL for women). The serum concentrations of creatinine and urea were assessed using various colorimetry methods by commercial kits (Pars Azemoon, Tehran, Iran) with the aid of a Selectra 2 Autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Serum albumin and TIBC were measured using a Pars Azmun Kit (Tehran, Iran) with the use of an automated analyzer (Selectra XL, ELITech Group, Puteaux, France). Dialysis adequacy based on Kt/V index was determined for each patient by a Kt/V calculator software using information recorded in patient files, including pre-dialysis blood urea nitrogen level, post-dialysis blood urea nitrogen level, the dialysis session length, post-dialysis weight, and ultrafiltration volume [14].

Statistical analyses

The normal distribution of the variables was checked by Shapiro–Wilk's *W* test. Continuous variables were summarized as mean (SD) if normally distributed or median (interquartile range IQR) if not normally distributed. In addition, categorical variables were reported as number (percentage). Continuous variables among groups were examined using an independent sample *t* test. Univariate logistic regression analysis was applied to estimate the association between the presence of PEW and other variables. Furthermore, to eliminate potential confounders, those variables with a significance level < 0.2 were entered into multiple logistic regression model. The association between PEW and other variables was examined in four different regression models. Significance was assumed at a p value less than 0.05. The statistical analyses were conducted using the SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc, Chicago, IL, USA).

Results

The study was conducted with 90 patients (39 males and 51 females). The mean age of patients was 46.64 ± 10.69 years. Among 90 patients, renal failure etiologies included diabetes mellitus ($n = 44$, 48.8%), chronic glomerulonephritis ($n = 8$, 8%), hypertension ($n = 45$, 45.5%), polycystic kidney disease ($n = 8$, 8%), urinary stone ($n = 14$, 15.5%), drug abuse ($n = 3$, 3%) and unknown ($N = 15$, 17%). The mean dialysis vintage of patients was 6.50 ± 5.37 years. We divided our patients according to MIS score into two subgroups. While 72.3% of patients were considered well nourished (MIS < 5), 27.7% of them were moderately malnourished (MIS ≥ 5). The ratios of patients according to MIS results are given in Table 1. Serum uric acid, hs-CRP, IL-6, endotoxin, albumin,

Table 1 Baseline characteristics of patient groups based on MIS score

Parameters	MIS < 5 $N = 65$	MIS ≥ 5 $N = 25$	Total $N = 90$	*p* value
Age, years	47 (38, 57.4)	48 (39, 57)	47 (38, 58)	0.580
Gender, no. (%)				0.24
Female	35 (53.8%)	16 (64%)	51 (56%)	
Male	30 (46.2%)	9 (36%)	39 (43.3%)	
Diabetes, no. (%)	34 (58.4%)	10 (40%)	44 (48.8%)	0.07
Hypertension, no. (%)	30 (46.1%)	11 (44%)	45 (45.5%)	0.65
Hemodialysis vintage, years	5.7 (1.2, 11.5)	6.5 (1.9, 12.3)	5.9 (1.4, 11.4)	0.27
Kt/V	1.46 (0.28)	1.44 (0.22)	1.45 (0.26)	0.88
BUN, mg/dL	53.5 (40.5, 71.5)	55 (43.5, 74.5)	55.0 (41.5, 73.5)	0.791
CR, mg/dL	6.1 (2.9)	5.9 (2.68)	6.1 (2.8)	0.492
Uric acid, mg/dL	6.6 (2.29)	8.7 (2.27)	7.1 (2.4)	0.002
Calcium, mg/dL	8.7 (0.81)	8.6 (0.82)	8.7 (0.8)	0.690
Phosphate, mg/dL	6.1 (1.94)	6.07 (1.97)	6.1 (1.9)	0.992
HB, g/dL	10.7 (1.80)	10.18 (1.74)	10.6 (1.8)	0.140
IL-6, pg/ml	35.15 (26.1, 48.9)	57 (33.3, 61.2)	35.6 (30.5, 54.5)	0.006
hs-CRP, mg/dL	6.48 (5.39, 8.05)	8.97 (7.4, 12.6)	7.36 (5.54, 8.9)	0.003
Endotoxin, IU/L	622.8 (160.86)	779.9 (200.9)	656.1 (180.7)	0.040
BMI, kg/m^2	23.84 (3.95)	17.60 (0.84)	22.52 (4.3)	< 0.001
Albumin, g/dL	3.94 (0.55)	3.7 (0.32)	3.8 (0.52)	< 0.001
anti.Hsp70, ng/ml	258 (175.5, 387)	492 (458.5, 531)	275 (188, 429)	< 0.001

BUN blood urea nitrogen, *CR* creatinine, *Hb* hemoglobin, *hs-CRP* high sensitivity C-reactive protein, *IL-6* interleukin-6, *BMI* body mass index, *anti-Hsp70* anti-heat shock protein 70

Data are mean ± SD or median (25th, 75th percentiles) and anti-Hsp70 levels were significantly higher and BMI and albumin were significantly lower in moderately malnourished patients compared to the well-nourished patients ($p < 0.05$) (Table 1).

Association of anti-Hsp70 levels with PEW (MIS ≥ 5) in HD patients

Furthermore, to investigate the association of anti-Hsp70 level and PEW (MIS ≥ 5) in HD patients, logistic regression analysis were performed. The univariate logistic regression model showed a significant association between PEW syndrome and the level of BMI, serum albumin, uric acid, hs-CRP, IL-6, endotoxin and anti-Hsp70 levels ($p < 0.05$). No significant association was found between serum anti-Hsp70 levels and clinical characteristics such as age, gender, presence of hypertension, and diabetes mellitus ($p > 0.05$). Most importantly, no association with serum BUN, CR, and phosphate was observed ($p > 0.05$) (Table 2).

We examined the possible effect of four models (Model 1: diabetes mellitus, albumin, hemodialysis vintage, BMI; Model 2: Model 1 + hs-CRP and IL6; Model 3: Model 2 + endotoxin; Model 4: Model 3 + uric acid) on the odds ratio. After correction for those major confounding factors, the significant association between malnutrition and circulating anti-Hsp70 remained significant (Table 3).

Table 2 Association between MIS ≥ 5 (moderately malnourished) using unadjusted logistic regression models

Variables	Univariate regression			
	OR	CI		*p*
		Lower	Upper	
Age, years	1.00	0.95	1.05	0.97
Gender, no. (%)	0.53	0.18	1.55	0.25
Diabetes, no. (%)	2.72	0.88	8.36	0.08
Hypertension, no. (%)	1.26	0.45	3.5	0.65
Hemodialysis vintage, year	1.7	0.85	3.3	0.12
BUN, mg/dL	1.00	0.97	1.03	0.60
CR, mg/dL	0.97	0.86	1.17	0.77
Uric acid, mg/dL	*1.46*	*1.15*	*1.85*	*0.002*
Calcium, mg/dL	0.80	0.43	1.47	0.82
Phosphate, mg/dL	0.97	0.74	1.26	0.82
Hb, g/dL	0.82	0.6	1.11	0.26
IL-6, pg/ml	*1.055*	*1.017*	*1.094*	*0.005*
hs-CRP, mg/dL	*1.21*	*1.043*	*1.42*	*0.002*
Endotoxin, IU/L	*1.005*	*1.002*	*1.008*	*0.002*
Albumin, g/dL	*0.175*	*0.06*	*0.49*	*0.001*
BMI, kg/m^2	*1.055*	*1.017*	*1.094*	*0.005*
anti.Hsp70, ng/ml	*1.016*	*1.009*	*1.024*	*<0.001*

BUN blood urea nitrogen, *CR* creatinine, *Hb* hemoglobin, *hs-CRP* high sensitivity C-reactive protein, *IL-6* interleukin-6, *BMI* body mass index, *anti-Hsp70* anti-heat shock protein 70

B unstandardized regression coefficients, *CI* confidence interval, *p* value refers to association between cachexia and other variables

Italicized data indicate statistical significance

Discussion

To the best of our knowledge, this is the first study to evaluate the association between the MIS score and serum level of anti-hsp70 in HD patients. In this cross-sectional study, we found that patients with higher MIS had higher serum level of anti-hsp70. Each one-point increment in MIS score was associated with higher serum anti-hsp70 level. This association remained significant after multivariable adjustments. In this study, serum anti-Hsp70 levels were markedly higher in patients with MIS score > 5 than those with MIS score < 5. The groups of patients with high and low MIS score were compared using logistic regression models adjusted for the following variables: diabetes mellitus, hemodialysis vintage, BMI, albumin, hs-CRP, IL6, and endotoxin levels. Furthermore, the lack of significant association was observed between serum anti-Hsp70 and serum creatinine and serum BUN, indicating that the elevation of serum anti-Hsp70 parallel with PEW is not due to the impaired renal clearance of anti-Hsp70. Here, we reported that 27.7% of our HD patients had an MIS score higher than 5, which is known as PEW syndrome that is associated with the inflammatory markers. In fact, the increase in the release or activation of pro-inflammatory cytokines such as IL-6 or TNF-α, as well as acute phase protein CRP, may suppress appetite and cause muscle proteolysis and hypoalbuminemia [15]. On the other hand, in HD patients cell damage or necrosis due to uremic toxins, inflammation, and high oxidative stress can lead to a release of intracellular HSP, which contributed to elevating HSP serum concentrations that initialize a response by

Table 3 Association between MIS ≥ 5 (moderately malnourished) and serum anti-hsp70 level using unadjusted and adjusted logistic regression models

Odds of malnutrition (MIS ≥ 5) (odds ratio and 95% confidence intervals)		*p* value
Unadjusted model	1.016 (1.009–1.024)	< 0.001
Model 1	1.016 (1.008–1.025)	0.001
Model 2	1.014 (1.005–1.024)	0.002
Model 3	1.014 (1.005–1.024)	0.004
Model 4	1.018 (1.006–1.030)	0.002

Odds ratio and 95% confidence intervals (CI) were obtained by logistic regression model

Model 1: diabetes mellitus, albumin, body mass index, hemodialysis vintage, Model 2: Model 1 + endotoxin, Model 3: Model 2 + hs-CRP and IL6, Model 4: Model 3 + uric acid the innate immune system [5]. Clinical and epidemiological studies have shown the higher levels of serum Hsp70 in hemodialysis patients [7, 16]. Serum Hsp70 works through binding to surface receptors (CD14, CD36, CD40, CD91, LOX-1, Toll-like receptor 2 and 4) on antigen-presenting cells, stimulating their pro-inflammatory cytokine (TNF-α, IL-1β, IL-6, and IL-12), as well as co-stimulatory molecule expression [5]. It has to be noted that elevated circulating Hsp70 levels were associated with inflammatory responses in several pathological conditions, such as acute infections, after liver resection and coronary artery bypass grafting, following myocardial infarction, HEELP syndrome, type 2 diabetes, preeclampsia, and during aging [8, 9, 11, 12, 17]. Therefore, circulating anti-Hsp70 might play a role in the development of the exaggerated systemic inflammatory response, which seems to be responsible for PEW progression in HD patients. To our state of knowledge, this is the first study evaluating serum anti-Hsp70 in HD patients suffering from malnutrition and correlating these data with other biochemical serum levels.

Further, some recent studies have shown the extracellular Hsp72 as a potential biomarker of sarcopenia [18], for which higher levels were found significantly associated with lower muscle mass, independently of age, sex, and the incidence of related diseases. Ogawa et al. found significant negative correlations between the percentage of changes in muscle thickness and cytokines (TNF-α and CRP), indicating that the increase in muscle thickness was associated with a decrease in TNF-α and CRP [19]. They stated that the reduction in serum Hsp72 level might reflect a decrease in systemic inflammation, which in turn would explain the increase in muscle thickness. Beyer et al. reported significant positive correlations between cytokines and serum Hsp70, suggesting that high levels of serum Hsp70 can reflect higher and less controlled inflammation activity with detrimental effect on muscle mass [20]. These data suggest that serum anti-Hsp70 and their antibodies, muscle mass, and systemic inflammation share some interactions, even though the underlying mechanisms need to be elucidated. Here, we have demonstrated the appearance of an independent positive association between serum anti-Hsp70 and PEW in HD patients. However, we have not evaluated body composition. To find out if anti-Hsp70 has an independent role in incident PEW or it only reflects the inflammatory state, we adjusted the association between PEW and anti-Hsp70 for hs-CRP, IL-6, uric acid, and endotoxin, which still remained significant. We also adjusted the presence of diabetes mellitus, BMI, albumin, and hemodialysis vintage as the logistic regression had shown that PEW is associated with them. Previous studies have shown that diabetes and insulin resistance are important contributing factors to PEW development [21]. In addition, renal failure progression and hemodialysis procedure for a long time had an additive effect on oxidative stress and inflammation, which may lead to the association of longer hemodialysis vintage with PEW progression. The role of longer dialysis vintage in PEW progression has been reported previously [22].

Interestingly, in the present study, we found that the mean age of patients (46.64 ± 10.69) was lower than that of the general HD population. The first explanation is that in the present study, in addition to diabetes and hypertension progressing to ESRD, a significant percent of HD patients had unknown etiology (17%) in contrast to developed country, in agreement with previous epidemiological studies in Iran [23–25]. Moreover, a significant percent of HD patients had urinary stone (15.5%) as their ESRD etiology. Statistical investigations relating to the prevalence of urinary stones in different parts of Iran represent the high prevalence of this incidence in the south and southwest (such as Khuzestan province) parts of Iran [26]. It could be as a result of high ambient temperature [27] and accumulation of toxic elements in the environment [28] in Khuzestan province, the tropical area of Iran. Therefore, a large percent of HD patients might have suffered from ESRD at a younger age in the present study.

There are several strengths and weaknesses of our study. The strengths of our study are the use of alternative statistical approaches to test our hypothesis, adjusting for important confounders, and separately analyzing for the presence of PEW. However, some important limitations of our study should be recognized. The first is our inability to infer causality from the observed associations because of inherent cross-sectional and observational studies design. Second, we did not assess body fat or body composition, so a definite association between body composition and serum anti-Hsp70 needs further research. Third, although the patients were included in the present study by random sample method, there are some concerns about generalization of the study sample to the HD population, because we primarily limited the study sample based on our inclusion and exclusion criteria, which these criteria were important to be controlled as the confounders in the present study. Therefore, the generalizability of our findings was restricted and the interpretation of results should be cautious.

In conclusion, these original data suggest that serum anti-Hsp70 levels may be associated with malnutrition in HD patients independently of the condition of the kidney, inflammation, diabetes mellitus, and hemodialysis vintage proven by a multiple logistic regression model. However, further prospective studies involving intervention trials should be conducted to search for actual causality relationship between them.

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Compliance with ethical standards

Conflict of interest Dr. Neda Haghighat declares that she has no competing interests.

Ethical approval All procedures performed in this study were in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Ahvaz University of Medical Sciences (IR.AJUMF.REC.1395.812).

Informed consent Informed consent was obtained from all patients included in the study.

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