Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1409090

# Determining the levels of serum Heat Shock Protein B7 (HSPB7) and tetranectin in patients undergoing hemodialysis

## *Hemodiyaliz tedavisi alan hastalarda serum Isı Şok Proteini B7 (HSPB7) ve tetranektin düzeylerinin belirlenmesi*

Özgen Kılıç Erkek, Gülşah Gündoğdu, Davut Akın, Mehmet Alpua, Dilek Sayın, Melek Bor Küçükatay

Posted date:03.01.2024 Acceptance date:19.02.2024

**Abstract**

**Purpose:** Heart damage may develop over time in patients with chronic renal disease (CKD), who are undergoing hemodialysis (HD) treatment. Serum levels of heat shock protein B7 (HSPB7) and tetranectin proteins change following damage to the heart muscle. This study aimed to determine HSPB7 and tetranectin levels in patients with CKD undergoing HD treatment.

**Materials and methods:** The patients aged 30-60 years old, healthy controls (n=30) and HD patients (n=30) participated in the study. Blood samples were taken from healthy subjects who applied to the hospital for check-up and from patients with kidney disease receiving HD treatment. Biochemical parameters were examined from the blood taken. HSPB7 and tetranectin levels from isolated serum samples were determined using measurement kits based on the solid phase sandwich (ELISA) principle.

**Results:** There was no significant difference between the groups in gender, age, glucose and iron (Fe) values of the subjects ($p$>0.05). Lymphocyte, platelet counts, hemoglobin and albumin values were found to be lower in patient group compared to the control group ($p$<0.05). Urea, creatine kinase (CK) and C-reactive protein (CRP) values were found to be higher in patient group than in the control group ($p$<0.05). A significant increase in HSPB7 levels and a significant decrease in tetranectin levels were detected in patient group compared to control group ($p$<0.001).

**Conclusions:** In this study, the changes detected in HSPB7 and tetranectin levels in with CKD undergoing HD treatment. May be early indicators of the possible development of cardiovascular diseases in patients with renal disease.

**Keywords:** Hemodialysis, chronic renal disease (CKD), HSPB7, tetranectin.

Kilic Erkek O, Gundogdu G, Akin D, Alpua M, Sayin D, Bor Kucukatay M. Determining the levels of serum Heat Shock Protein B7 (HSPB7) and tetranectin in patients undergoing hemodialysis. Pam Med J 2024;17:337-345.

**Öz**

**Amaç:** Kronik böbrek hastalığı olan ve hemodiyaliz (HD) tedavisi alan hastalarda zamanla kalp hasarı gelişebilmektedir. Isı şok proteini B7 (HSPB7) ve tetranektin proteinlerinin serum düzeyleri kalp kasında gelişen hasarı takiben değişmektedir. Bu çalışmada, HD tedavisi alan KBH hastalarında HSPB7 ve tetranektin düzeylerinin araştırılması amaçlanmıştır.

**Gereç ve yöntem:** Çalışmaya 30-60 yaş, sağlıklı ve HD hastası denekler katılmış olup iki grup oluşturulmuştur (n=60): Kontrol grubu (n=30) ve Hasta grubu (n=30). Hastaneye check-up için başvuran sağlıklı deneklerden ve böbrek hastalığı olup HD tedavisi alan hastalardan kan örnekleri alınmıştır. Alınan kanlardan biyokimyasal parametreler incelenmiştir. İzole edilen serum örneklerinden HSPB7 ve tetranektin düzeyleri solid faz sandwich (ELİSA) prensibine dayanan ölçüm kitleri kullanılarak belirlenmiştir.

**Bulgular:** Deneklerin cinsiyet, yaş, glukoz ve Demir (Fe) değerlerinde gruplar arasında anlamlı fark saptanmamıştır ($p$>0,05). Lenfosit, trombosit sayıları, hemoglobin ve albümin değerleri diyaliz hastalarında kontrol grubuna kıyasla düşük bulunmuştur ($p$<0,05). Diyaliz hastalarında üre, kreatin kinaz ve CRP değerleri sağlıklı kontrol grubuna göre yüksek saptanmıştır ($p$<0,05). Hastalarda sağlıklı deneklere kıyasla, HSPB7 düzeylerinde anlamlı artış ve tetranektin düzeylerinde ise anlamlı düşüş tespit edilmiştir ($p$<0,001).

Özgen Kılıç Erkek, Asst. Prof. Department of Physiology, Pamukkale University, Faculty of Medicine, Denizli, Türkiye, e-mail: oerkek@pau.edu.tr (https://orcid.org/0000-0001-8037-099X) (Corresponding Author)

Gülşah Gündoğdu, Assoc. Prof. Department of Physiology, Pamukkale University, Faculty of Medicine, Denizli, Türkiye, e-mail: ggundogdu@pau.edu.tr (https://orcid.org/0000-0002-9924-5176)

Davut Akın, Assoc. Prof. Pamukkale University, Faculty of Medicine, Division of Nephrology, Denizli, Türkiye, e-mail: dakin@pau.edu.tr (https://orcid.org/0000-0002-9567-7940)

Mehmet Alpua, Asst. Prof. Department of Gastroentereology, Pamukkale University, Faculty of Medicine, Denizli, Türkiye, e-mail: malpua@pau.edu.tr (https://orcid.org/0000-0002-2359-007X)

Dilek Sayın, M.D. Department of Physiology, Pamukkale University, Faculty of Medicine, Denizli, Türkiye, e-mail: dsayin@pau.edu.tr (https://orcid.org/0000-0003-4022-874X)

Melek Bor Küçükatay, Prof. Department of Physiology, Pamukkale University, Faculty of Medicine, Denizli, Türkiye, e-mail: mbor@pau.edu.tr (https://orcid.org/0000-0002-9366-0205)

**Sonuç:** Bu çalışmada, diyaliz tedavisi alan KBH hastalarında HSPB7 ve tetranektin düzeylerinde tespit edilen değişimler, böbrek yetmezliği olan hastalarda olası gelişebilecek kardiyovasküler hastalıkların gelişiminin erken göstergesi olabilir.

**Anahtar kelimeler:** Hemodiyaliz, kronik böbrek hastalığı (KBH), HSPB7, tetranektin.

Kılıç Erkek Ö, Gündoğdu G, Akın D, Alpua M, Sayın D, Bor Küçükatay M. Hemodiyaliz tedavisi alan hastalarda serum Isı Şok Proteini B7 (HSPB7) ve tetranektin düzeylerinin belirlenmesi. Pam Tıp Derg 2024;17:337-345.

## Introduction

Chronic kidney disease (CKD) is a pathology that arises from the irreversible loss of kidney functions affecting many organ systems [1]. In CKD, chronic and progressive deterioration is observed in the kidney's fluid-solute balance and metabolic-endocrine functions due to the decrease in glomerular filtration rate (GFR). When the GFR value decreases to 5-15 ml/min/1.73m^2, it is referred to end-stage kidney failure (ESKF), and patients require renal replacement therapies such as dialysis or renal transplantation [2]. The life expectancy of patients has begun to increase, and their quality of life has started to improve with Dialysis technology. Hemodialysis (HD) is preferred in the treatment of ESKF, which is resistant to medical treatment, and when the GFR value falls below 10 ml/min [3]. HD is a therapeutic procedure where blood taken from the patient is filtered through a semi-permeable membrane using a device, homogenized with dialysate coming from the opposite direction, and then returned to the patient, regulating acid-base, electrolyte, and toxic substances [4].

Patients with CKD are at high risk for cardiovascular disease (CVD) even in the early stages of the disease. The risk of CVD in patients with ESKF is reported to be 10-20 times higher than the general population [5]. Clinically, in these patients, the risk of developing CVD, and early death increases with decreased kidney functions and the presence of albuminuria. Studies have shown a relationship between the decrease in GFR and CVD (congestive heart failure, myocardial infarction (MI), stroke, peripheral vascular disease, etc.). Moreover, a positive correlation between the progression of CKD and cardiovascular risk has been identified [6]. Therefore, more than 50% of HD patients develop CVD, increasing the risk of death [7, 8]. Thus, the development of CVD in patients with ESKF undergoing HD treatment becomes one of the main causes of morbidity and mortality [9].

Heat shock protein beta-7 (HSPB7) is a cardiovascular heat shock protein preserved α-crystalline in its C-terminal region [10]. The HSPB7 protein interacts with filamin C, playing a significant role in the formation of actinin in the cell skeleton and anchoring actin filaments to the cell membrane. In the absence of this protein, filamin C separates from its location in the cell, leading to structural damage in the cell membrane [11]. HSPB7 primarily functions as ATP-independent molecular chaperones that assist in the formation of the cell skeleton, suppress the accumulation of stress-resistant and denatured proteins [12]. It binds denatured proteins and facilitates their proteolytic degradation by transporting them to other heat shock proteins with ATPase activity, proteasomes, or autophagosomes [13]. The highest protein level of HSPB7 has been detected in heart tissue, and its mutations have been associated with heart diseases [14]. Therefore, serum HSPB7 levels increase when released from cardiomyocytes as a result of myocardial damage [15, 16].

Tetranectin, with the gene name CLEC3B, is a calcium-binding homotrimeric protein from the C-type lectin protein family [17]. It interacts with a range of cellular factors, including plasminogen, apolipoprotein A1, and heparin. It has a protective function in muscle, bone, and circulatory systems. Additionally, it is observed in serum and extracellular matrix (ECM) during tissue regeneration [18]. Tetranectin plays significant roles in binding ECM components (fibrin, plasminogen), stimulating the proteolytic activation of proteases and growth factors, and regulating ECM proteolysis during tissue reshaping [19]. A negative correlation has been shown between serum tetranectin levels and the development of CVD [20].

Although in the literature, there are various studies that demonstrated the association of HSPB7 and tetranectin with CVDs, there is no study in the literature evaluating the relationship between HSPB7 and tetranectin levels in patients with CKD that are at high risk of developing CVD. In this context, this study aims to determine the levels of HSPB7 and tetranectin in patients with CKD undergoing HD treatment.

## Material and methods

### Formation of experimental groups

### Sample

A total of 60 subjects aged between 30-60 years participated in the study and were divided into two groups: control group (n=30) and patient group (n=30). The study included healthy volunteers with normal check-up results who visited the nephrology department of Pamukkale University Hospital for health screening purposes and patients diagnosed with CKD receiving hemodialysis treatment. Patients were selected from those routinely undergoing HD treatment at Pamukkale University Hospital, while patients receiving peritoneal dialysis or kidney transplant recipients were excluded from the study. In addition to these, patients have not been diagnosed with MI in the last 6 months, severe valve disease, chronic heart failure, coronary artery disease, atrial fibrillation, coronary bypass, and malignancy excluded from study. The control group for the study included subjects without any additional diseases and with CKD (GFR>60 ml/min/1.73 m^2).

### Collection and storage of blood samples from participants

In the study, serum samples of patients and healthy volunteers who visited the hospital simultaneously were collected at the time of hospital admission following a 12-hour fasting period. In both groups, parameters such as hemoglobin (Hb), glucose, urea, creatine kinase (CK). C-reactive protein (CRP), albumin, iron (Fe), leukocyte count, neutrophil count, lymphocyte count, neutrophil lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR) were requested from blood test results. A blood sample taken in a 2 ml biochemistry tube was used for the determination of serum tetranectin and HSPB7 levels. Within 15 minutes, it was centrifuged at 3500 rpm for 10 minutes at room temperature, and the obtained serums were stored at -80°C until the day of analysis.

### Determination of serum tetranectin and HSPB7 levels by ELISA method

After allowing the serum samples to reach room temperature, serum tetranectin (E6262Hu, BT lab) and HSPB7 (E5380Hu, BT lab) levels were determined by comparing with reference samples using commercial kits and the ELISA method.

### Statistical evaluation

The effect size obtained from reference study was found to be quite strong (d=0.957) [21]. Assuming that we could obtain a lower level of power, a power analysis was conducted, and it was calculated that when at least 60 individuals (at least 30 for each group) were included in the study for an effect size of d=0.8, a power of 80% could be achieved at a 95% confidence level. All calculations for power analysis were performed using the GPower package program (version 3.1.9.2. HeinrichHeine-Universitat, Dusseldorf, Germany).

For statistical comparison of demographic and laboratory parameters from patient and control groups. Shapiro wilk test were used for determination of normal distribution. If parametric test conditions were satisfied. Independent samples t test was used for comparisons among groups. If parametric test conditions were not satisfied, Mann Whitney U-Test was used and associations between categorical variables were evaluated using the chi-square test ($\chi^2$ test). All analyses were performed using SPSS 24 software for statistical analysis. Results were presented as mean ± standard deviations and $p \leq 0.05$ was considered as statistically significant. Ethical approval was obtained from the Pamukkale University Medical Ethics Committee.

## Results

### Evaluation of demographic and laboratory parameters of the participants

When the gender and age values of the participants were compared, no statistically significant differences were found between the control group and the dialysis patient group

($p$>0.05). There was no statistically significant difference between the patient and control groups in Fe values ($p$>0.05). However, Hb ($p$=0.001) and albumin ($p$=0.003) values were lower, while glucose ($p$=0.003), urea ($p$=0.001), CK ($p$=0.001), and CRP ($p$=0.029) values were found to be higher in patient group compared to the control group (Table 1).

**Table 1.** Demographic and laboratory parameters of the subjects and control

| | Control (n=30) | Patient (n=30) | Test Statistics | |
|---|---|---|---|---|
| | | | Test value | *p* value |
| **Men (%)** | 44.8% | 55.2% | $\chi^2$=0.739 | 0.39 |
| **Age** | 44.76±1.83 | 44.54±0.87 | t=0.106 | 0.916 |
| **Hemoglobin (Hb) (g/dL)** | 13.88±.47 | 11.14±0.42 | t=4.340 | **0.001**** |
| **Glucose (mmol/L)** | 92.12±2.58 | 155.29±20.76 | t=-3.080 | **0.001**** |
| **Urea (mg/dL)** | 25.72±1.52 | 125.83±6.16 | t=-16.076 | **0.001**** |
| **Creatine Kinase (CK) (U/L)** | 0.80±0.033 | 8.27±0.49 | t=-15.483 | **0.001**** |
| **C-reactive protein (CRP) (mg/L)** | 2.98±0.58 | 13.60±4.78 | t=-2.249 | **0.029*** |
| **Albumin (g/L)** | 44.86±0.64 | 37.52±2.17 | t=3.298 | **0.003*** |
| **Iron (Fe) (µg/dL)** | 77.06±6.13 | 69.54±5.29 | t=0.926 | 0.359 |

Results are given as mean ± standard deviation, n=30, t: Independent-samples *t* test, $\chi^2$: Chi-Square test statistics
*: $p$<0.05 indicates a significant difference from the control group, **: $p$<0.01 indicates a significant difference from the control group
Hgb: Hemoglobin, CK: Creatine Kinase, CRP: C-reactive protein, Fe: Iron

## Biochemical findings

Table 2 shows the biochemical parameters of the control and patient group. No statistically significant differences were detected between the groups in NLR, PLR, neutrophil, and leukocyte counts ($p$>0.05). Lymphocyte and platelet counts were statistically significantly lower in dialysis patients group compared to the control group ($p$=0.009 and $p$=0.001, respectively).

**Table 2.** Biochemical parameters of control and dialysis patients

| | Control (n=30) | Patient (n=30) | Test Statistics | |
|---|---|---|---|---|
| | | | Test value | *p* value |
| **Neutrophil count (K/µL)** | 4.28±0.21 | 3.92±0.30 | t=0.972 | 0.336 |
| **Lymphocyte count (K/µL)** | 2.31±0.09 | 1.89±0.12 | t=2.713 | **0.009**** |
| **NLR: Neutrophil/Lymphocyte Ratio** | 1.89±0.090 | 2.29±0.21 | t=-1.736 | 0.089 |
| **PLR: Platelet/Lymphocyte Ratio** | 126.30±8.054 | 116.06±12.37 | t=0.699 | 0.488 |
| **Leukocyte count (K/µL)** | 7.22±0.273 | 6.98±0.37 | t=0.498 | 0.621 |
| **Platelet count (K/µL)** | 281.24±14.99 | 195.12±11.38 | t=4.547 | **0.001**** |

Results are given as mean ± standard deviation; n=30, t: Independent-samples *t* test , **: $p$<0.01 difference from the control group
NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio

## Determination of serum tetranectin and HSPB7 concentrations

The serum tetranectin level was determined using an ELISA kit in ng/mL. The serum tetranectin level was found to be statistically significantly lower in the patient group (63.50±24.21) compared to the control group (84.17±42.45) (z=-2.764, $p$=0.006) (Figure 1). The serum HSPB7 level was determined using an ELISA kit in ng/mL. The serum HSPB7 level was found to be statistically significantly higher in the patient group (10.50±5.20) compared to the control group (5.90±1.39) (z=4.558, $p$=0.001) (Figure 2).

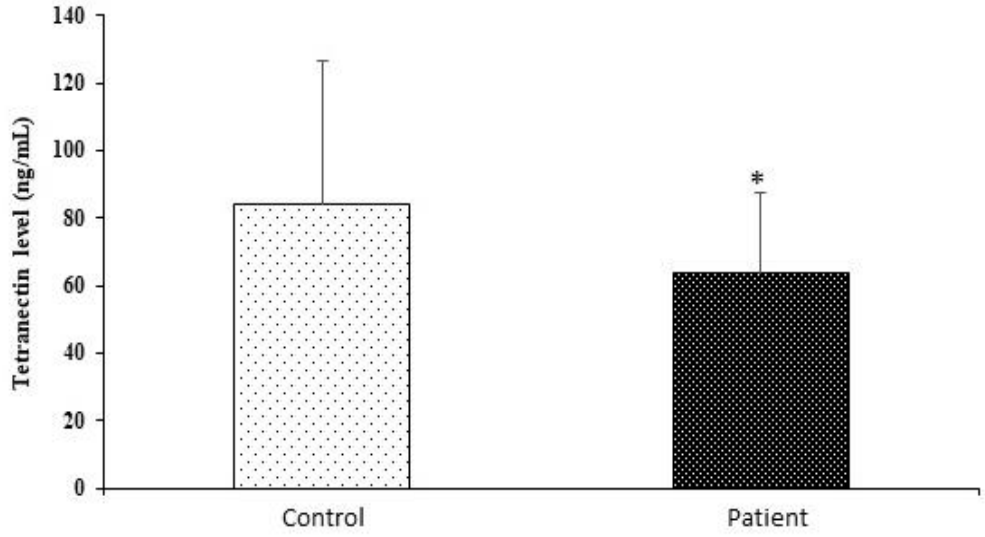


**Figure 1.** Serum tetranectin levels in control group and dialysis patients (ng/mL)

Mean ± standard deviation; n=30, Mann Whitney U-Test was used
*: Significant difference from the control group at $p<0.01$ level

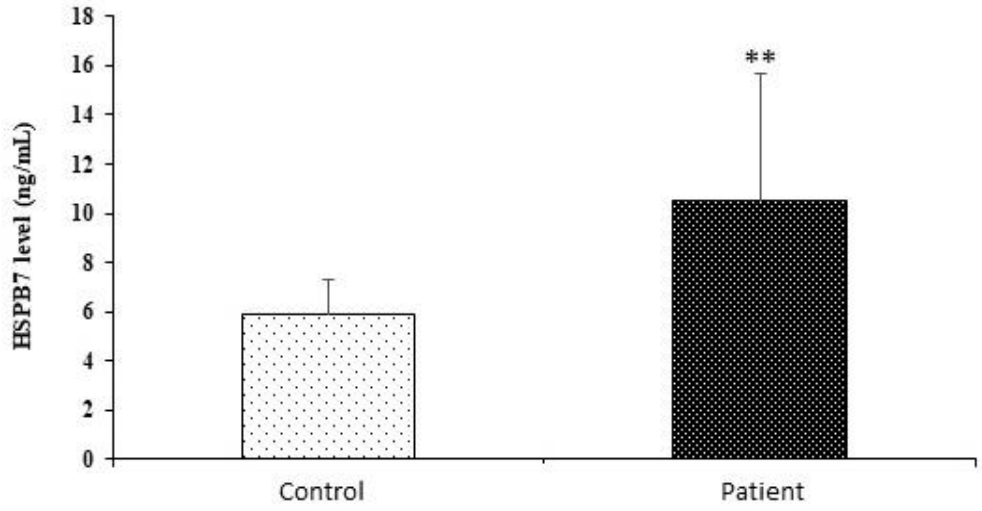


**Figure 2.** Serum HSPB7 levels in control group and dialysis patients (ng/mL)

Mean ± standard deviation; n=30, Mann Whitney U-Test was used
*: Significant difference from the control group at $p<0.001$ level

## Discussion

In this study, our aim was to demonstrate the changes in the serum level of HSPB7 and tetranectin, cardiac-spefic proteins, in CKD patients undergoing HD. We found that HSPB7 protein level of CKD patients undergoing HD was high in the serum, while the tetranectin protein was low compared to healthy individuals. Additionally, we reported that laboratory parameters as Hb, albumin, lymphocyte, and platelet levels were decreased, and glucose, urea, CK, CRP values were increased in the HD patients.

Patients with CKD undergoing HD have a significantly higher risk of CVD than the general population, and approximately 50% of the causes of death are due to CVDs. Progressive destruction of renal parenchyma and loss of

functional nephrons are characteristic of CKD pathology [2]. The most important indicator of CKD is the irreversible decrease in GFR over time. In today's diagnosis of CKD, many laboratory parameters, especially GFR levels in the blood, are important [22].

It is known that inflammation plays a significant role in the mortality of HD patients and HD treatment itself increases the production of inflammatory mediators in CKD patients [23]. In recent years, due to the advantage of easily obtaining routine hemogram and laboratory parameters without adding an economic burden, they have become the focus of researchers as indicators of inflammation. Among these parameters, CRP is a parameter that indicates inflammation in patients undergoing HD treatment, and a positive correlation has been detected between CRP levels and the development of CVD [24].

In studies conducted, it has been shown that in patients undergoing HD treatment CRP increases and albumin decreases, and Alanli et al. [24] have suggested that these parameters can be used to evaluate the risk of mortality in HD patients [25]. In this study, in line with the literature, it was found that CRP levels were high and albumin levels were low in CKD patients undergoing HD treatment compared to controls.

Another laboratory finding is that CK isoenzyme and urea levels are high in patients with CKD undergoing HD treatment [26]. In this study, in line with the literature. CK and urea levels were found to be statistically significantly higher in CKD patients undergoing HD treatment compared to controls.

Platelets, one of the routine hemogram parameters, secrete inflammatory mediators and growth factors taking part in hemostasis, inflammation, and tissue repair [27]. A decrease in lymphocyte count is observed in many inflammatory diseases. NLR is a hemogram parameter obtained by dividing the number of neutrophils by lymphocytes. In previous studies, it has been reported that NLR has a negative correlation with GFR, a positive correlation with the stage of CKD, and thrombocytopenia is observed in patients undergoing HD treatment [28]. In this study, in line with the literature, it was found that lymphocyte and platelet levels were statistically significantly lower and NLR levels increased in CKD patients undergoing HD treatment compared to controls.

Studies have shown that CVDs can develop in CKD patients undergoing HD treatment. Ng et al. [8] reported a significant increase in cardiac mortality in patients undergoing HD treatment with CKD. In patients with CKD undergoing HD treatment, it is thought that HD treatment can lead to the development of CVD due to a decrease in perfusion of vital organs (heart, intestines, kidneys, and brain) and can also be considered as a reason for progressive dysfunction in the cardiovascular system due to an increase in arterial pressure and total blood volume [29, 30].

HSPs, which constitute approximately 10% of all cellular proteins, have the main function of preventing the accumulation of denatured proteins and controlling protein homeostasis [31]. It has been found that they increase not only in response to increased temperature but also to many adverse conditions such as toxins, inflammation, ischemia, and hypoxia [32]. The expression of HSPB7 increases under different adverse stress conditions. HSPB7 can participate in the selective degradation of denatured proteins in autophagosomes, control the redox state, and assemble and protect the cell skeleton [33]. Data obtained from studies have characterized HSPB7 as a protein mainly expressed in the heart and named it as a cardiac heat shock protein. It has been concluded that HSPB7 affects cardiac morphogenesis and can accompany congenital and acquired heart diseases [34]. HSPB7 stabilizes by binding to sarcomeric proteins and maintains contraction integrity [14]. In addition, it is necessary for the growth of ventricular cardiomyocytes to maintain the number and size of cells [34]. Loss of HSPB7 protein from cardiac tissue leads to irregularities in myofibrils and disruption of the sarcolemma structure. When HSPB7 is released from muscle tissue, its levels increase in the serum. On the other hand, the expression of HSPB7 protein in muscle tissue prevents the apoptosis of myocardial cells by providing reoxygenation and protects the heart from the harmful effects of ischemia-reperfusion [35]. In the study conducted by Liao et al. [36], they found that the dislocation of HSPB7 resulted in the disruption of the gap-junction complex and intercalated disc structures in cardiomyocytes.

This led to a decrease in the expression of connexin 43 and mislocalization of N-cadherin and desmoplakin proteins, inducing arrhythmic sudden death. In this study, it has been demonstrated that serum HSPB7 levels in CKD patients undergoing HD treatment have significantly increased compared to the control group. This finding suggests that the increase in the HSPB7 protein in muscle tissue may be due to potential damage that could have developed in cardiomyocytes as a result of HD treatment.

Tetranectin is a type C lectin that specifically binds to the plasminogen kringle-4 domain, thereby enhancing plasminogen activation, making it an endogenous ligand [37]. It primarily plays a role in tissue remodeling and development [38]. Tetranectin released from platelets possesses anti-thrombotic properties (through increased plasminogen activation) and anti-proliferative characteristics (associated with endothelium) [39]. One of the most significant effects of tetranectin is to support better blood circulation in the heart muscles. In a study conducted by Yin et al. [39], it was found that tetranectin levels were inversely proportional to the risk of cardiovascular events (CVD), and Chen et al. [40] found lower serum tetranectin levels in relation to the prognosis of coronary artery disease. In this study, it was demonstrated that serum tetranectin levels in CKD patients undergoing HD treatment have significantly decreased compared to the control group. This finding suggests that the decrease in this heart-specific protein may result from potential damage that could occur in cardiomyocytes as a result of HD treatment.

In conclusion, despite some limitations in this study, it was determined for the first time that serum HSPB7 levels increased and tetranectin levels decreased in CKD patients undergoing HD treatment. As a result, our findings suggest that changes in these proteins specific to the heart muscle may serve as indicators for potential CVD developments that are important in terms of morbidity and mortality in CKD patients receiving HD treatment.

There are certain limitations to our study. The study was conducted based on a single center, and patients from other centers were not included. Although a larger sample could not be examined, power analysis was performed, and an adequate number of patients were included accordingly. In future studies, monthly follow-ups can be conducted during hemodialysis treatment in CKD patients, allowing the observation of changes in these proteins over time, and confirming the ELISA results with RT-PCR.

**Conflict of interest:** No conflict of interest was declared by the authors.

## References


1. Okpechi IG, Nthite T, Swanepoel CR. Health-related quality of life in patients on hemodialysis and peritoneal dialysis. Saudi J Kidney Dis Transpl 2013;24:519-526. https://doi.org/10.4103/1319-2442.111036
2. Vaidya SR, Aeddula NR. Chronic Kidney Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. 2022 Oct 24.
3. Elliott DA. Hemodialysis. Clin Tech Small Anim Pract 2000;15:136-148. https://doi.org/10.1053/svms.2000.18297
4. Pedersen JO, Knudsen F, Jersild C. Acute effect of hemodialysis on neutrophil migration: impact on humoral and cellular function. Kidney Int Suppl 1988;24:86-89.
5. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000;356:147-152. https://doi.org/10.1016/S0140-6736(00)02456-9
6. Li X, Lindholm B. Cardiovascular risk prediction in chronic kidney disease. Am J Nephrol 2022;53:730-739. https://doi.org/10.1159/000528560
7. Cozzolino M, Galassi A, Pivari F, Ciceri P, Conte F. The cardiovascular burden in end-stage renal disease. Contrib Nephrol 2017;191:44-57. https://doi.org/10.1159/000479250
8. Ng CH, Ong ZH, Sran HK, Wee TB. Comparison of cardiovascular mortality in hemodialysis versus peritoneal dialysis. Int Urol Nephrol 2021;53:1363-1371. https://doi.org/10.1007/s11255-020-02683-9
9. Mahmoodi BK, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. Lancet 2012;380:1649-1661. https://doi.org/10.1016/S0140-6736(12)61272-0
10. Janowska MK, Baughman HER, Woods CN, Klevit RE. Mechanisms of small heat shock proteins. Cold Spring Harb Perspect Biol 2019;11:a034025(e1-22). https://doi.org/10.1101/CSHPERSPECT.A034025
11. Juo LY, Liao WC, Shih YL, Yang BY, Liu AB, Yan YT. HSPB7 interacts with dimerized FLNC and its absence results in progressive myopathy in skeletal muscles. J Cell Sci 2016;129:1661-1670. https://doi.org/10.1242/jcs.179887

12. Sun Y, MacRae TH. The small heat shock proteins and their role in human disease. FEBS J 2005;272:2613-2627. https://doi.org/10.1111/j.1742-4658.2005.04708.x

13. Rusmini P, Cristofani R, Galbiati M, et al. The role of the heat shock protein B8 (HSPB8) in motoneuron diseases. Front Mol Neurosci 2017;21:10:176(e1-9). https://doi.org/10.3389/FNMOL.2017.00176

14. Juo LY, Liao WC, Shih YL, et al. HSPB7 interacts with dimerized FLNC and its absence results in progressive myopathy in skeletal muscles. J Cell Sci 2016;129:1661-1670. https://doi.org/10.1242/jcs.179887

15. Chiu TF, Li CH, Chen CC, et al. Association of plasma concentration of small heat shock protein B7 with acute coronary syndrome. Circ J 2012;76:2226-2233. https://doi.org/10.1253/circj.cj-12-0238

16. Chen FF, Xia YL, Xu CQ, et al. Common variant rs7597774 in ADD2 is associated with dilated cardiomyopathy in Chinese Han population. Int J Clin Exp Med 2015;8:1188-1196.

17. Tanisawa K, Arai Y, Hirose N, et al. Exome-wide association study ıdentifies clec3b missense variant p.s106g as being associated with extreme longevity in east asian populations. J Gerontol A Biol Sci Med Sci 2017;72:309-318. https://doi.org/10.1093/GERONA/GLW074

18. Christensen L, Clemmensen I. Differences in tetranectin immunoreactivity between benign and malignant breast tissue. Histochemistry 1991;95:427-433. https://doi.org/10.1007/BF00315737

19. Arellano Garcia ME, Li R, Liu X, et al. Identification of tetranectin as a potential biomarker for metastatic oral cancer. Int J Mol Sci 2010;11:3106-3121. https://doi.org/10.3390/IJMS11093106

20. Dardé VM, De La Cuesta F, Gil Dones F, Alvarez Llamas G, Barderas MG, Vivanco F. Analysis of the plasma proteome associated with acute coronary syndrome: does a permanent protein signature exist in the plasma of ACS patients? J Proteome Res 2010;9:4420-4432. https://doi.org/10.1021/pr1002017

21. Ghazavi A, Ganji A, Keshavarzian N, Rabiemajd S, Mosayebi G. Cytokine profile and disease severity in patients with COVID-19. Cytokine 2021;137:155323. https://doi.org/10.1016/j.cyto.2020.155323

22. Khan Z, Pandey M. Role of kidney biomarkers of chronic kidney disease: an update. Saudi J Biol Sci 2014;21:294-299. https://doi.org/10.1016/J.SJBS.2014.07.003

23. Wang Y, Gao L. Inflammation and cardiovascular disease associated with hemodialysis for end-stage renal disease. Front Pharmacol 2022;13:800950(e1-19). https://doi.org/10.3389/FPHAR.2022.800950

24. Alanli R, Kucukay MB, Mursel S, et al. Laboratory test paramaters and echocardiography findings that affect mortality in hemodialysis patients. Ankara Egt Ars Hast Derg 2022;56:74-77. https://doi.org/10.20492/aeahtd.1019834

25. Ma L, Zhao S. Risk factors for mortality in patients undergoing hemodialysis: A systematic review and meta-analysis. Int J Cardiol 2017;238:151-158. https://doi.org/10.1016/j.ijcard.2017.02.095

26. Jaffe AS, Ritter C, Meltzer V, Harter H, Roberts R. Unmasking artifactual increases in creatine kinase isoenzymes in patients with renal failure. J Lab Clin Med 1984;104:193-202.

27. Moro García MA, Mayo JC, Sainz RM, Alonso Arias R. Influence of Inflammation in the Process of T Lymphocyte Differentiation: Proliferative, Metabolic, and Oxidative Changes. Front Immunol 2018;9:00339(e1-18). https://doi.org/10.3389/FIMMU.2018.00339

28. Hakim RM, Schafer AI. Hemodialysis-associated platelet activation and thrombocytopenia. Am J Med 1985;78:575-580. https://doi.org/10.1016/0002-9343(85)90398-5

29. Buchanan C, Mohammed A, Cox E, et al. Intradialytic cardiac magnetic resonance imaging to assess cardiovascular responses in a short-term trial of hemodiafiltration and hemodialysis. J Am Soc Nephrol 2017:28:1269-1277. https://doi.org/10.1681/ASN.2016060686

30. Kanda H, Hirasaki Y, Iida T, et al. Perioperative management of patients with end-stage renal disease. J Cardiothorac Vasc Anesth 2017;31:2251-2267. https://doi.org/10.1053/j.jvca.2017.04.019

31. Morimoto RI. Cell-nonautonomous regulation of proteostasis in aging and disease. Cold Spring Harb Perspect Biol 2020;12:a034074. https://doi.org/10.1101/CSHPERSPECT.A034074

32. Doran P, Gannon J, O'Connell K, Ohlendieck K. Aging skeletal muscle shows a drastic increase in the small heat shock proteins αB-crystallin/HspB5 and cvHsp/HspB7. Eur J Cell Biol 2007;86:629-640. https://doi.org/10.1016/j.ejcb.2007.07.003

33. Muranova LK, Shatov VM, Bukach OV, Gusev NB. Cardio-Vascular Heat Shock Protein (cvHsp, HspB7), an unusual representative of small heat shock protein family. Biochemistry (Moscow) 2021;86:1-11. https://doi.org/10.1134/S0006297921140017

34. Rosenfeld GE, Mercer EJ, Mason CE, Evans T. Small heat shock proteins Hspb7 and Hspb12 regulate early steps of cardiac morphogenesis. Dev Biol 2013;381:389-400. https://doi.org/10.1016/J.YDBIO.2013.06.025

35. Liu L, Zhang X, Qian B, et al. Over-expression of heat shock protein 27 attenuates doxorubicin-induced cardiac dysfunction in mice. Eur J Heart Fail 2007;9:762-769. https://doi.org/10.1016/j.ejheart.2007.03.007

36. Liao WC, Juo LY, Shih YL, Chen YH, Yan YT. HSPB7 prevents cardiac conduction system defect through maintaining intercalated disc integrity. PLoS Genet 2017;13:e1006984. https://doi.org/10.1371/JOURNAL.PGEN.1006984

37. Mogues T, Etzerodt M, Hall C, Engelich G, Graversen JH, Hartshorn KL. Tetranectin binds to the kringle 1-4 form of angiostatin and modifies its functional activity. J Biomed Biotechnol 2004;2004:73-78. https://doi.org/10.1155/S1110724304307096

38. Jaquinod M, Las Holtet T, Etzerodt M, Clemmensen I, Thøgersen HC, Roepstorff P. Mass spectrometric characterisation of post-translational modification and genetic variation in human tetranectin. Biol Chem 1999;380:1307-1314. https://doi.org/10.1515/BC.1999.166

39. Yin X, Subramanian S, Hwang SJ, et al. Protein biomarkers of new-onset cardiovascular disease: a prospective study from the Systems Approach to Biomarker Research in Cardiovascular Disease (SABRe CVD) initiative. Arterioscler Thromb Vasc Biol 2014;34:939-945. https://doi.org/10.1161/ATVBAHA.113.302918

40. Chen Y, Han H, Yan X, et al. Tetranectin as a potential biomarker for stable coronary artery disease. Sci Rep 2015;1:17632. https://doi.org/10.1038/SREP17632

**Ethics committee approval:** Ethical approval was obtained from the Medical Ethics Committee of Pamukkale University (approval date 13.09.2022/13, decision no: E-60116787-020-263897). Informed voluntary consent forms were obtained from the subjects regarding the study.

**Authors' contributions to the article:** Conceptualization: O.K.E. and G.G. Literature Review: O.K.E., G.G. and D.S. Design: O.K.E., G.G. and M.B.K. Data Collection: D.A. and M.A. Analysis and Interpretation: O.K.E. and G.G. Manuscript Writing: O.K.E., G.G., D.A., D.S., M.A. and M.B.K. Critical Review: D.A., G.G. and M.B.K.