



Effects of HBV and HCV infection on oxidative stress and inflammation in hemodialysis patients

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Abstract

Background and purpose: Chronic renal failure is a syndrome characterized by progressive and irreversible loss of nephrons depending on various diseases. Especially infection such as HBV and HCV is among the major causes of mortality and morbidity in hemodialysis patients. In the present study we aimed to determine the levels of 3-nitrotyrosine (3-NT), TNF-like weak inducer of apoptosis (TWEAK) and heat shock protein (HSP70) in chronic renal failure patients diagnosed with HBV, HCV and non-hepatitis undergoing hemodialysis treatment.

Materials and methods: Samples of 235-patients receiving hemodialysis treatment and 25-healthy individuals were included in the study. Firstly, HBV and HCV positivity were diagnosed by serological Enzyme-Linked Immunosorbent Assay (ELISA) method. Then, 3-NT levels were determined using High-Performance Liquid Chromatography (HPLC), while TWEAK and HSP70 were determined using high sensitivity ELISA. The numbers of patients used in the studies were determined according to statistical power analysis.

Results: The values of 3-NT and HSP70 were found to be significantly higher non-hepatitis patients, HBV and HCV patients receiving hemodialysis treatment to compared with the control group ($p < 0.05$). Concentration of TWEAK in non-hepatitis and HBV patients receiving hemodialysis therapy was found to be significantly higher to compared with the control group ($p < 0.05$). However, unlike the other two groups, an increase in the TWEAK of HCV patients on post-dialysis was determined.

Conclusions: To prevent the increase of inflammation and oxidative stress in hemodialysis patients or to keep it under control, investigating certain parameters such as TWEAK, 3-NT and HSP70 from time to time is of great importance in terms of minimizing the level of risk for many diseases such as cardiovascular diseases. Infection also increases the burden on oxidative stress and immunity system in these patients.

INTRODUCTION

Some changes occur in several clinical and laboratory findings in patients due to loss of in the kidneys. These findings increase based on how progressive the loss of function is and they are classified into four stages (1). Terminal period, the fourth one, is the uremia and during this period, patients need renal replacement therapies such as dialysis or transplantation. Hemodialysis patients in the terminal stage are quite susceptible to various infections, particularly viral infections, particularly (2). Hepatitis B (HBV) and hepatitis C (HCV) viruses which

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are major health problems in all societies are also seen frequently in hemodialysis patients. Several factors are known to be associated with increased risk of HBV and HCV infections. Duration on HD is well recognized as an important predisposing factor for HBV and HCV. It is estimated that over two billion people are infected with HBV worldwide (3). Compared with other viruses transmitted by blood, HBV is highly contagious (5). However, approximately 1.75 million people were newly infected with HCV in 2015, thus bringing the global total of people living with HCV to 71 million (4–6). In studies conducted in recent years, it has been reported that HBV and HCV infections have a high incidence in patients undergoing chronic hemodialysis therapy (2, 7–10). This is both due to the weak immune systems and a large number of parenteral interventions during treatment (7, 8). Especially, they do not respond sufficiently to vaccinations thymus-dependent antigens, such as HBV (1, 9–11). The most important ways of transmission of HCV in dialysis units are contaminated materials, insufficiently trained cleaning staff and vials being used on multiple patients (12). However, it is not known what precautions are taken to protect these patients from viral agents such as HBV and HCV (2). The longer the duration of dialysis in hemodialysis patients, the higher the frequency of HBV and HCV incidence rises significantly in the same way (13–15). A major chronic reduction in antioxidant systems and an increase in the formation of oxygen free radicals are both encountered in dialysis patients and in patients with hepatitis (16). It is observed that free oxygen radicals are overproduced in organisms, while antioxidant mechanism remains inadequate, disrupting the balance which means that oxidative stress occurs. Studies in recent years indicate that the increased oxygen free radicals and lipid peroxidation play a part in the development of many diseases (17–19). Normally antioxidant defense and reactive oxygen species in the human body are in balance. Intensive production of reactive oxygen species or the decline of antioxidant defense creates oxidative stress by causing structural and functional changes in biomolecules (19, 20). Studies conducted so far suggest, it has been seen that hemodialysis therapy applied for end-stage chronic renal failure patients leads to increased oxidative stress (21–23). In recent years, 3-nitrotyrosine (3-NT) is used as a marker to evaluate potential cytotoxic effects of NO in the organism. Peroxynitrite (NO⁻) is a cytotoxic derivative occurring as a result of reactions of with nitric oxide (NO) and O₂ in the living beings (24). Another important marker for oxidative stress and immunity is the TNF-like weak inducer of apoptosis (TWEAK), a member of the TNF family. It has many functions similar to TNF- α . TWEAK in cytokine family stimulates apoptosis, while at the same time it induces inflammation and cell growth. Another marker exhibiting an increase under stress heat shock protein HSP70. The increase occurring in HSP70 offers protection for cell culture and animal tissues (25). Also, HSP70

helps proteins to be transported in cells and has a function in the folding of proteins synthesized within the cell and it is responsible for the destruction of unstable proteins as well as preventing protein aggregation and it also helps protein folding refold when damaged and apoptosis (26).

In our study, in addition to investigating the prevalence of viral infections (HBV and HCV), one of the major problems encountered in hemodialysis patients receiving dialysis treatment due to chronic renal failure, we also aimed to evaluate the effect of infection on oxidative stress and protein oxidation. For this purpose, 3-NT, TWEAK and HSP70 levels were investigated in the control group and chronic renal failure patients on hemodialysis therapy.

MATERIALS AND METHODS

Patients Selection Criteria

Ethical approval for the study was obtained from local ethics committee (University of OMU Protocol No. 107/2012). Two hundred thirty-five patients receiving hemodialysis therapy due to chronic renal failure in Corum private dialysis centers were involved in the study. The numbers of patients with HBV and HCV infections and non-hepatitis receiving hemodialysis treatment included in the study were based on the power analysis. The patients were classified into different groups based on the presence of viral coinfections as well. Serum samples of 235 patients receiving hemodialysis treatment due to chronic renal failure and 25 individuals as healthy control group were included in the study. Patients included in this analysis ranged in age from 25 to 65 years old, with a median age of 45. Serum was obtained by centrifugation of whole blood at 3000 rpm for 10 min and aliquots were stored at -80 °C until assayed.

Diagnosis of HCV and HBV infections

HBV and HCV positivity were determined by serological ELISA method. HBsAg ELISA kits (ABOTT PRISM HBsAg, USA) for HBV and Murex anti-HCV ELISA kits (ABBOTT murex, South Africa) for HCV were used.

Protein Damage Index: Determination of 3-nitrotyrosine levels

Determination of 3-NT levels, the protein damage indicator in the serum sample of patients and healthy individuals included in the study, was done using HPLC (Immuchrom, Haasen, Germany) kit in HPLC system (High-Performance Liquid Chromatography).

Determination of TWEAK and HSP70 levels

High-sensitivity ELISA kit was used to determine the level of the Human TWEAK instant and Human soluble

Table 1. 3-NT values (µg/L) of non-hepatitis, HBV and HCV patients receiving hemodialysis treatment and control group

Groups	n	Mean ± S.D.	95% Confidence Interval for Mean Min. – Max.
Control	25	13.08 ± 4.65	11.16 – 15.00
HBV			
Pre-HD	25	124.62 ± 33.65*	110.73 – 138.51
Post-HD	25	21.72 ± 7.46*	18.64 – 24.80
HCV			
Pre-HD	25	257.22 ± 25.05*	246.88 – 267.57
Post-HD	25	34.80 ± 17.25*	27.68 – 41.92
Non-Hepatitis			
Pre-HD	25	211.16 ± 35.88*	196.35 – 225.97
Post-HD	25	42.03 ± 16.12*	35.37 – 48.68

HD; Hemodialysis

Values are expressed as mean ± S.D.

* Statistical significance level was determined as p <0.05 when both control and intra-group comparisons were made. (p=0.000 for HBV, HCV and non-hepatitis)

HSP70 (Bendermed Diagnostic System, eBioscience, Austria, Avicer to, eBioscience, Inc., respectively).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (IBM SPSS Inc. Chicago, IL, USA). All mea-

surements were taken in triplicate. Data are reported as mean± standard distribution (SD). After assessing the normality distribution (Shapiro-Wilk test) and homogeneity of variances, parametric t-test and ANOVA were used. In cases where these assumptions were not met, non-parametric Mann Whitney-U and Kruskal Wallis H-tests were used for comparison of differences between means. The critical significance level for the statistical tests performed was set at 0.05.

RESULTS

HBV and HCV positivity were investigated in all samples through ELISA method. According to the results, the rate of HBV was 22.5 % (53/235), the rate of HCV was 10.6 % (25/235), while 66.8 % (157/235) of patients were not infected with HCV or HBV .

Evaluation of 3-NT

The level of 3-nitrotyrosine, which is the protein damage indicator, was found to be significantly higher non-hepatitis patients, hepatitis B and hepatitis C patients receiving hemodialysis treatment than the control group (p<0.05). 3-NT values of patients with HCV in pre-hemodialysis were found higher than those of HBV and non-hepatitis group. Although a significant decrease could be observed on post-dialysis when the pre and post-dialysis 3-NT values were compared in all samples, still the values obtained were higher compared with the control group as indicated in Table 1 and Figure 1.

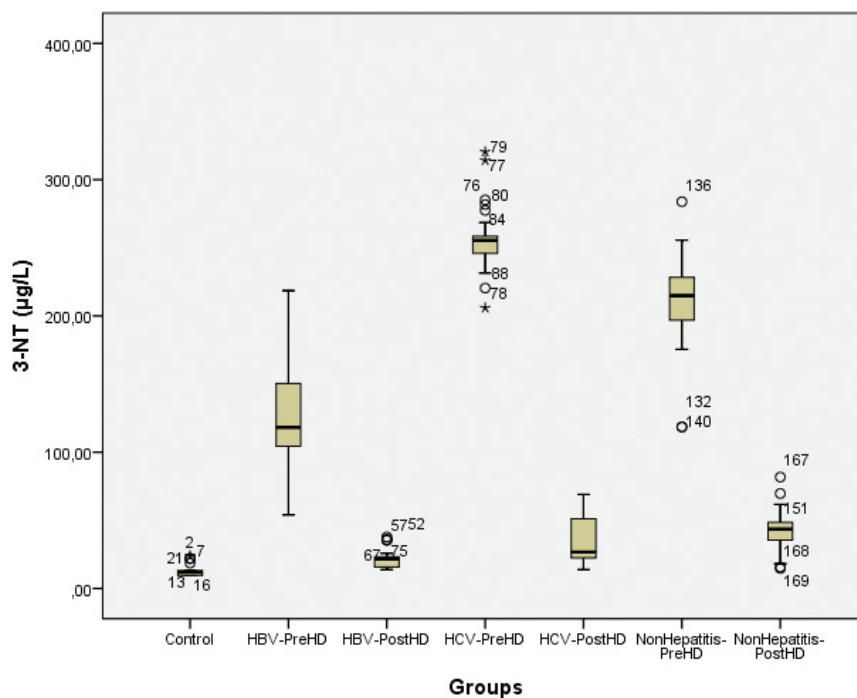


Figure 1. 3-NT levels, the protein damage index of non-hepatitis, hepatitis B and hepatitis C patients receiving hemodialysis treatment and control group.

Table 2. TWEAK values (pg/ml) of non-hepatitis, HBV and HCV patients receiving hemodialysis treatment and control group

Groups	n	Mean ± S.D.	95% Confidence Interval for Mean Min. – Max.
Control	25	335.7 ± 49.2	315.4 – 356.0
HBV			
Pre-HD	25	773.8 ± 452.6*	587.0 – 960.7
Post-HD	25	380.8 ± 68.8*	352.4 – 409.2
HCV			
Pre-HD	25	181.2 ± 54.9*	158.6 – 203.9
Post-HD	25	462.2 ± 140.7*	404.0 – 250.2
Non-Hepatitis			
Pre-HD	25	989.2 ± 234.6*	892.4 – 1086.1
Post-HD	25	429.1 ± 104.3*	386.0 – 472.1

HD; Hemodialysis

Values are expressed as mean ± S.D.

* Statistical significance level was determined as $p < 0.05$ when both control and intra-group comparisons were made. ($p=0.016$ for HBV, $p=0.000$ for HCV and non-hepatitis)

Evaluation of TWEAK

TWEAK values in non-hepatitis and HBV patients receiving hemodialysis therapy were found to be significantly higher compared with controls ($p < 0.05$). Although

a significant decrease could be observed in non-hepatitis and HBV patients groups in post-dialysis when the pre and post-dialysis values were compared, the values could still be observed to be above the control group. However, unlike the other two groups, an increase in the TWEAK values of HCV patients on post-dialysis was determined. TWEAK values of all groups were given in Table 2 and Figure 2.

Evaluation of HSP-70

The HSP-70 values were found to be higher in non-hepatitis, HBV and HCV patients receiving hemodialysis therapy than those of control group. When pre and post-dialysis values are compared, a minimal increase in post-dialysis among HBV, HCV and non-hepatitis patient groups was observed (Table 3, Figure 3). Statistical significance level was determined as $p < 0.05$ when both control and intra-group comparisons were made. But when the intra-group comparison was made, the statistical significance level was determined as $p > 0.05$ only on HBV group.

DISCUSSION

Hemodialysis is an effective treatment for most patients with renal failure and an alternative for kidney transplantation, thereby improving the quality of life of the patient with adequate dialysis and even prolongs the lifespan (27). However, among the most important factors leading to an increase in mortality rate and restricting the quality of life

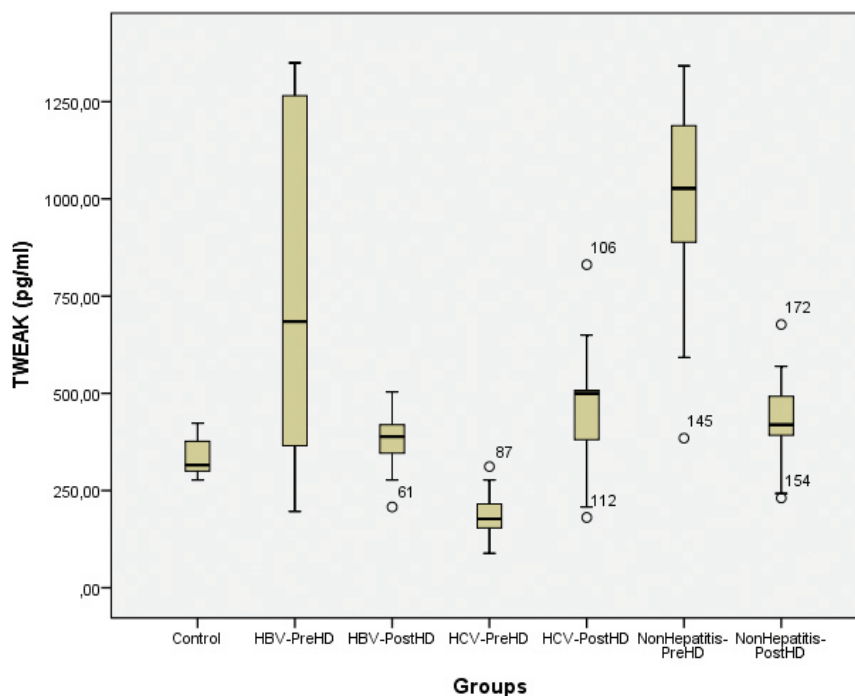
**Figure 2.** TWEAK levels of non-hepatitis, hepatitis B and hepatitis C patients receiving hemodialysis treatment and control group

Table 3. HSP-70 values (pg/ml) of non-hepatitis, HBV and HCV patients receiving hemodialysis treatment and control group

Groups	n	Mean ± S.D.	95% Confidence Interval for Mean Min. – Max.	p
Control	25	3.3 ± 0.3	3.2 – 3.4	
HBV**				
Pre-HD	25	11.8 ± 2.6*	10.7 – 12.9	*
Post-HD	25	12.6 ± 3.9*	11.0 – 14.5	*
HCV				
Pre-HD	25	9.7 ± 1.0*	9.3 – 10.2	*
Post-HD	25	10.8 ± 1.7*	10.1 – 11.6	*
Non-Hepatitis				
Pre-HD	25	9.9 ± 1.3*	9.4 – 10.4	*
Post-HD	25	10.8 ± 1.4*	10.2 – 11.4	*

HD; Hemodialysis

Values are expressed as mean ± S.D.

* Statistical significance level was determined as p <0.05 when both control and intra-group comparisons were made. (p=0.011 for HCV and p=0.031 for non-hepatitis)

** But when the intra-group comparison was made, the statistical significance level was determined as p > 0.05 only on HBV group. (p=0.751 for HBV)

in dialysis patients during the dialysis are viral diseases. In particular, HBV and HCV are serious public health problems in the world; moreover, patients with chronic kidney

disease are exposed to these infections at a very high rate (7, 8). The compromised immune systems of the dialysis patients with dialysis might lead to other disorders in other body functions. Vascular calcification and oxidative stress are widely encountered especially among patients receiving hemodialysis developing end-stage renal disease (ESRD). In addition to investigating the prevalence of viral infections (HBV and HCV), one of the major problems encountered in hemodialysis patients receiving dialysis treatment due to chronic renal failure, we also aimed to evaluate the effect of infection on oxidative stress and protein oxidation in this patient group through various parameters. For this purpose, by determining the 3-NT, TWEAK and HSP70 levels, these levels were compared both with the control and patient groups. The level of 3-NT, the oxidative stress indicator, in these patients was also investigated by Erdur et al. to determine the relationship between coronary artery calcification and oxidative stress in peritoneal dialysis and hemodialysis patients and it was found that the level of nitrotyrosine was higher compared to healthy individuals (28). Koleganova et al. immunohistochemically determined the level of TNF-alpha and nitrotyrosine in aortic samples of ESRD and control group. ESRD patients on TNF-alpha and nitrotyrosine levels were found to be significantly higher compared to the control group (29). In the results part of the study in which Köse et al aimed to determine the effects of hemodialysis and peritoneal dialysis treatments on oxidative and nitrosative stress markers, they concluded that pre and post hemodialysis high plasma 3-NT levels could indicate a significantly increased risk for nitrosative tissue damage in these patients. Kose et

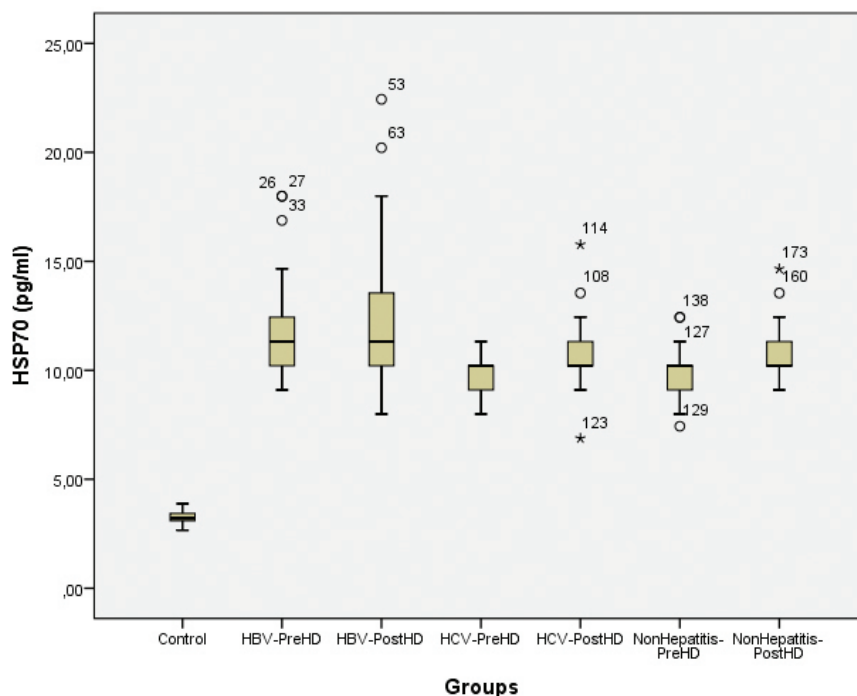


Figure 3. HSP-70 levels of non-hepatitis, hepatitis B and hepatitis C patients receiving hemodialysis treatment and control group

al, in their study, intended to determine the effect of hemodialysis and peritoneal dialysis treatments on oxidative and nitrosative stress markers revealed that high presence of 3-NT levels pre and post hemodialysis indicate significantly increased the risk for nitrosative tissue damage in these patients (30). It was found in a study carried out by Proddi et al that 3-NT levels in CKD and ESRD patients were significantly higher compared to healthy subjects (31). In a study by Qian et al which aimed to investigate the relationship between the level of protein damage indicator 3 NT and mortality in patients receiving treatment due to kidney damage. Therefore, 90-day mortality rates of patients treated for kidney damage and 3-NT levels were recorded and compared. The level of 3-NT in patients with kidney damage was found significantly higher compared to healthy control subjects. It was also found that high 3-NT levels in patients are also proportional to high mortality rates (32). Oxidative stress is one of the potential biochemical mechanisms of chronic viral pathogenesis. In his study In an another study, Namiduru et al measured malondialdehyde, myeloperoxidase and nitrotyrosine levels in chronic HBV and HCV patients in order to determine the level of oxidative stress. No statistically significant difference between patients with hepatitis and control group was observed in nitrotyrosine levels. The data obtained from this study has shown that there is oxidative stability in patients with chronic viral disorders (33). In our study, 3 NT levels were found statistically significantly higher in pre dialysis of non-hepatitis, HBV and HCV patients receiving hemodialysis treatment statistically significantly higher than the control group. Despite the reduction in 3-NT levels post dialysis they still did not reach the value of healthy individuals. Considering the values obtained from the study, it has been established that protein oxidation caused by 3-NT and a cytotoxic effect was higher HCV patients among other patient groups. In recent years, although it has been known that TWEAK, a glycoprotein found in the TNF superfamily, has a relation with atherosclerosis, endothelial dysfunction and mortality in renal and non-renal patients, the results obtained vary from each other. Increased levels of TWEAK are observed in clinical conditions caused by inflammatory events, while TWEAK level decreases in atherosclerosis, which indicates that the event could be different depending on the interaction in receptor levels (34). In our study, the increase and reduction in TWEAK levels of HBV and HCV patients compared to the control are thought to be caused by receptor difference which plays a significant role in the viral interaction. Kralish et al in a study determined TWEAK levels in healthy control group, TWEAK levels in hemodialysis patients also in diabetic patients on hemodialysis therapy and found that TWEAK levels significantly reduced in diabetic patients receiving hemodialysis treatment and also concluded that TWEAK could be a risk factor for atherosclerosis (35). Yilmaz et al. studied how patients with non-diabetic chronic renal failure undergo changes in TWEAK levels

in different stages and also investigated whether there is a relationship between TWEAK levels and endothelial dysfunction. It was found that as the stage of renal failure increases, there is an increase in endothelial dysfunction as opposed to the decrease in TWEAK level and it was also concluded that TWEAK is independent of endothelial dysfunction (36). In our study, it was observed that the high TWEAK value pre-dialysis, which is a marker of inflammation, decreased the following dialysis in HBV and non-infective patient groups, but it was determined not to be enough. As for HCV patients, while their pre dialysis TWEAK levels were lower compared to healthy subjects, these values increased post dialysis and passed the TWEAK values of healthy subjects. Inflammation in HCV patients was observed to increase rapidly with dialysis. Another parameter associated with oxidative stress is heat shock protein HSP70 and it can also be detected in diseases such as tissue, cell or serum levels of cardiovascular diseases, diabetes or diseases such as hyperlipidemia, and obesity (37). Yabunak et al found that HSP70 levels of diabetic patients in mononuclear cells which were measured by Western blot method was higher than in healthy controls, but stated that it has no connection with HbA1c and fasting blood glucose (38). In spite of various diseases in the literature to be working with a group of diseases with similar levels of HSP70, it was determined and found to be higher in the presence of oxidative stress. In the literature reviews done, although there was no study with similar disease groups, HSP70 levels were detected in some diseases and found to be higher in the presence of oxidative stress (26, 39, 40). In our study, a statistically significant increase pre and post dialysis in HSP70 levels of the patient groups and the HSP70 levels belonging to the healthy control group was observed. However, a statistically significant change was determined between the groups.

CONCLUSIONS

Renal failure is a disease that manifests itself in the deterioration of the essential functions of the kidneys that cause damage to the individual at a significant level, which is accompanied by a decrease in glomerular filtration value. Although this damage, which occurs in the kidneys, is tried to be alleviated by dialysis treatment, it also increases the oxidative stress and immunity in the patients.

Viral diseases are frequently seen in patients undergoing hemodialysis treatment. Increased viral load in these patients increases the oxidative burden in the organism with renal failure.

In our study, 3-NT, TWEAK and HSP 70 values were higher in patients without hepatitis compared to the control group, indicating that oxidative stress and immunity increased in patients and that they could not be sufficiently reduced by dialysis treatment. In addition to dialysis, the presence of HBV alone and HCV alone in these

patients affects different levels of oxidative stress and immunity in patients. The presence of HCV alone increased the levels of 3-NT and HSP in the patients and caused a decrease in the TWEAK values.

To prevent the increase of inflammation and oxidative stress in hemodialysis patients or to keep it under control, investigating certain parameters such as TWEAK, 3-NT and HSP70 from time to time is of great importance in terms of minimizing the level of risk for many diseases such as cardiovascular diseases.

Infection also increases the burden on oxidative stress and immunity system in these patients. This study emphasizes that the important of infection in dialysis patients who have a high mortality and morbidity rate.

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