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Effect of Increased Blood Flow Velocity on Fatigue in Hemodialysis Patients

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Abstract

Background: Fatigue is one of the outcomes of reduced dialysis adequacy (DA) in patients undergoing hemodialysis (HD). Accordingly, increased blood flow velocity (BFV) can be one of the strategies to enhance DA and reduce fatigue.

Aim: This study aimed to determine the effect of increased BFV on fatigue in HD patients.

Method: This two-group randomized clinical trial was conducted on 74 HD patients attending 17-Shahrivar Hospital and Shafa Dialysis Center, Mashhad, Iran, during 2018. The intervention group was subjected to 25 and 50 rounds, which were added to the mean value calculated for dialysis machine velocity. Considering the control group, the rounds of the machine were set as those mean of the first two sessions. Fatigue was measured using the standardized Multidimensional Fatigue Inventory. The blood urea nitrogen (BUN) level and DA were analyzed after the 1st, 8th, and 14th sessions. The data were analyzed in SPSS software (version 16) through independent t-test, repeated measures analysis of variance (ANOVA), Mann-Whitney U test, and Chi-square test.

Results: The mean ages of the control and intervention groups were 57.16±13.81 and 55.86±13.56 years, respectively. The results of repeated measures ANOVA showed that fatigue in the intervention group had significantly dropped during HD sessions, compared to the control group. Moreover, these patients obtained better DA ($P<0.001$).

Implications for Practice: Increased BFV of the dialysis machine leads to improved DA, BUN removal, and reduced fatigue in HD patients, which can be recommended to nurses as an effective strategy.

Keywords: Blood flow velocity, Chronic kidney disease, Fatigue, Hemodialysis

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Introduction

The prevalence rate of chronic kidney disease (CKD) in Iran has been reported by 680 cases per one-million population (1) in a way that approximately 15% is annually added to these figures (2). Patients undergoing hemodialysis (HD) suffer from high fatigue with an incidence rate of 60-97% (3), and 70% of the cases are experiencing sudden extreme fatigue (4).

The NANDA International (formerly the North American Nursing Diagnosis Association) has accordingly defined fatigue as the development of asthenia, also known as weakness, lethargy, burnout, lack of energy, as well as a low capacity for physical and mental activities (5). The given complication does not have a single cause, and several factors might be involved in its development, especially in HD patients, including physiological changes (especially high blood urea nitrogen [BUN] levels and low hemoglobin count), medications and their side effects, nutritional deficiencies, and psychological factors, such as depression and sleep disorders (6).

This multidimensional phenomenon with its chronic and debilitating nature in patients undergoing HD can lead to a decline in self-care activities and limited role-plays, thereby reducing abilities in individuals to perform daily living activities in the event of being exacerbated and stabilized (7).

Attributable to the nature of the gradual onset of fatigue, the HD patients may assume this complication as a natural component of CKD and adapt with low levels of energy though they may not be aware of the severity of damages to themselves. Therefore, if nurses do not ask questions about this condition, this common problem remains unknown since patients might not speak a word of it (8). Fatigue in patients affected with CKD is far more important where 94% of these individuals are more inclined to increase their levels of energy through undergoing HD (9). As a result, assessment and management of fatigue are of significance in improving clinical performance and quality of life in these patients (10).

It is of note that fatigue can be reported as a whole or in multiple dimensions. Reports on fatigue dimensions can thus help have better management in this regard by obtaining more details of this phenomenon. In this respect, general fatigue (i.e., fatigue during individuals' daily activities), physical fatigue (i.e., bodily sensations), mental fatigue (cognitive symptoms in an individual), as well as fatigue due to reduced activity and motivation to start any other activities can be pointed out among the main dimensions (11).

Currently, pharmaceutical and non-pharmaceutical interventions are being applied to manage and treat fatigue. However, as cited in the related literature, numerous limitations and obstacles to the use of such treatments have drawn attention to fatigue as one of the factors agonizing HD patients (12). For instance, intravenous vitamin C as an effective drug in moderating fatigue (5) might be associated with complications, such as lysis of red blood cells and anemia, hyperuricemia, diarrhea, as well as nausea, and vomiting in these patients (13). Non-pharmaceutical interventions to treat fatigue (e.g. transcutaneous electrical acupoint stimulation [TEAS]) (6), progressive muscle relaxation (7), and sports (14) also have their limitations.

Accordingly, factors, such as a need for patients' active involvement, long-time patient training, no supervision on performing related home activities by a nurse (7, 15), and non-applicability of these methods for all HD patients (14) have been far taken into account as barriers to patients' failure in completing them. The presence of these shortcomings to make the best use of such procedures during HD has consequently led to considering other interventions to diminish fatigue in patients accompanied by minimal problems and complications.

As one of the duties of dialysis nurses is to set up dialysis machines, such as adjusting blood flow velocity (BFV), determining solution temperature, selecting filter type, and specifying dialysate solution osmolality (i.e., sodium concentration) (16), these individuals perform such set-ups concerning vital signs, patient tolerance, and monthly test results, including BUN, serum phosphorus, and potassium levels.

The BFV during HD indicates the volume of blood pumped through the arterial needle by the pump of the dialysis machine per minute of a patient's body into an arterial tube. The given amount is recommended between 200 and 500 cc/min based on the needle size used (17). An increase in the BFV of dialysis machines in a safe mode can be thus one of the interventions practiced by dialysis nurses during this procedure. Today, research is being conducted on the effects of increased BFV on dialysis adequacy (DA), BUN removal (18-21), HD complications (22, 23), sleep disorders, uremic pruritus (24), as well as mortality rate (25) in HD patients. According to these studies, increased BFV

has been able to enhance DA in such patients (18, 19).
It should be noted that uremic toxins are among the causes of protein-energy wasting, inducing fatigue, asthenia, and lethargy in HD patients. Since BUN clearance plays an important role in DA (17), it seems that increased BFV during HD followed by acceptable recovery and BUN clearance (18, 20) are expected to reduce fatigue, particularly in the dimensions of general fatigue and physical fatigue.
Since no study has been carried out so far to measure the effect of increased BFV in patients undergoing HD on fatigue, a question arises whether increased BFV reduces fatigue in HD patients or not and how much escalation can meet this objective. The present study aimed to determine the effect of increased BFV on fatigue in patients undergoing HD.

Methods
This clinical single-blind randomized controlled trial was conducted in 2018. The statistical population included HD patients attending 17-Shahrivar Hospital and Shafa Dialysis Center, Mashhad, Iran. It is worth mentioning that they were unaware of being assigned to control or intervention groups. Cohen's d based on at least 70% effect size, 95% confidence interval (CI), and 80% test power were used (26) to determine the sample size. The sample size was accordingly estimated to be 35 individuals in each group; however, taking the possibility of 10% sample attrition into account to achieve better results, the sample size was considered equal to 40 people in each group.
The participants were selected based on the inclusion criteria using a convenience sampling method. Subsequently, the simple random sampling method and random numbers were employed to assign them to intervention and control groups via the website www.randomization.com. This meant that numbers 1 to 100 were given to the software at the beginning and the first 50 random numbers were then assigned to the intervention group. Following that, the second 50 random numbers were placed in the control group. In the next stage, the first patient meeting the inclusion criteria was assigned with number 1 and this procedure continued until the sample size was completed. The number given to each participant was consequently checked in the list of random numbers. If the participants' codes were in the list of the numbers for the intervention group, the patients could be assigned to the intervention group. On the other hand, if the participants' codes were on the list of the numbers for the control group, the patients could be placed in the control group.
The inclusion criteria were: 1) ability to read and write, 2) minimum six months of HD, 3) three 4-h HD sessions a week, 4) arteriovenous fistula or graft, 5) no history of HD complications, such as impaired hemodynamics in the past months, 6) no development of chronic physical disorders (e.g., debilitating cardiovascular and respiratory diseases or stage-4 cancer approved by physicians working in relevant departments), 7) no amputated upper and lower extremities, 8) mean pump rounds of 300 and/or less than 300 (cc/min) in two sessions before sampling, and 9) development of no psychological disorders, such as severe depression.
On the other hand, the patients with severe anemia (hemoglobin concentraction<8 mg/dl), bleeding, and infection, as well as a crisis in the past six months, and those who underwent kidney transplant during the study and were hospitalized followed by some complications, such as increased BFV (e.g., restlessness, muscle cramps, nausea and vomiting, shortness of breath, and low blood pressure) along with the patients who were unwilling to continue the intervention were excluded from the study.
The data were collected using a demographic/disease characteristics form, patient records, laboratory test checklist, and the standardized Multidimensional Fatigue Inventory (MFI) to assess fatigue. The 20-item MFI included five separate dimensions of general, physical, and mental fatigue, as well as fatigue due to reduced activity and motivation. This questionnaire could be administered to a population of patients and healthy individuals. Each dimension was also comprised of four items scored on a 5-point Likert-type scale (minimum and maximum scores of 1 and 5, respectively). Therefore, the score of each dimension could be from 4 to 20, and the total score of the fatigue determined through the sum of scores from dimensions could be between 20 and 100.
The MFI was firstly developed by Smets in 1995, and its reliability was estimated at 0.84 using the Cronbach's alpha method (11). This researcher also administered the given questionnaire for the first time to patients with cancer undergoing radiation therapy and reported the range of Cronbach's alpha coefficient between 0.79 and 0.93 for different dimensions of fatigue (27). According to the MFI's

instructions, fatigue could be questioned in the last few days. This questionnaire has been also utilized on patients undergoing HD in several investigations in Iran (5, 28, 29, 30). In the present study, the reliability of the questionnaire was determined before the onset of the main study on 20 HD patients, and its Cronbach's alpha coefficient was obtained at 0.893. In addition, Cronbach's alpha coefficient for different dimensions of fatigue was calculated between 0.80 and 0.94.

To fulfill the research procedure, the researcher stayed on patients' bedside at the beginning of the study and obtained written consent from them. Subsequently, demographic/disease characteristics information form and patient records along with MFI were reviewed and completed. Afterward, in the first two sessions, the pump rounds of the dialysis machine (i.e. BFV) were recorded, and their mean values were calculated in this study.

After the random assignment of the participants to control or intervention group, 25 rounds were added to the mean BFV of the first two sessions from the 3rd to 8th sessions, and the MFI was completed at the end of the 8th session if the participants were in the intervention group. From the 9th to the 14th sessions, 50 rounds were also added to the initial BFV mean value. At the end of the 14th session, the MFI was re-completed by the participants. The BUN level, DA, as well as all patients' test results were correspondingly recorded in the 1st and the 14th sessions before and after HD. Considering DA (Kt/V), it was calculated and recorded based on the BUN levels before and after HD, HD time, and weight gain in patients between two sessions using the software available in the departments.

According to the guidelines of the Handbook of Dialysis by Daugerdas et al., acceptable pump velocity could be expressed based on the needle size applied. Following the instructions in this book, the permissible maximum pump velocity was 350 cc/min for needle size 16, which could be changed corresponding to the patient's tolerance (17). Given that needle size 16 was being used for all HD patients in the present study, they were allowed to have a maximum of 350 rounds in terms of velocity increase in the dialysis machine. However, based on the results of the studies, this change in the rounds of the machine was gradually adjusted regarding the initial round mean values for each patient (24).

As can be seen in Table 1, the maximum mean pump velocity in patients in the present study was less than 300 rounds, which was less than 350 rounds per minute (rpm) as the allowable velocity including an increase of 50 rounds. Therefore, according to the mean value of the two previous sessions, as the mean was less than 300, increased pump rounds for patients could be considered for two stages, namely, 25 and 50 rounds. During two weeks, increased pump rounds for 25 rpm, and in the next two weeks, 50 rpm was taken into account. This increasing trend was designed according to a previously conducted study (24).

If the participants were assigned to the control group, the pump rounds were the same as the mean value for the first two sessions as usual from the 3rd session to the 14th session. The MFI was also completed by the patients in the 1st session and at the end of the 8th and 14th sessions. The BUN level, DA, and patient's test results in the 1st and 14th sessions were also recorded in this study.

Given that the maximum BFV adjustable by the dialysis machine could depend on needle size used (17), the needle size for all patients was selected 16 in the dialysis departments of the present study. Accordingly, the maximum BFV of 350 cc/min was considered in this study (17).

All through the HD procedure, participants' hemodynamic status and clinical symptoms were carefully monitored every hour, and in case of hemodynamic disturbances and intolerance (i.e., severely low blood pressure, muscle cramps, nausea and vomiting, shortness of breath, and balance disorder), the BFV was reduced once again. If necessary, medical treatments were delivered to these patients, and they were excluded from the study.

In total, three participants in the control group were removed from the study due to death (n=1), kidney transplant (n=1), and hospitalization (n=1). Moreover, three participants in the intervention group were excluded from the study due to hospitalization (n=1), unwillingness to continue the study (n=1), and intolerance to increased pump rounds (n=1). Accordingly, 74 participants remained until the study was completed.

All the participants received HD through the Farzinius Medical Care dialysis machine with fixed bicarbonate solution and constant flow velocity of dialysis solution (for low flux filters of 500 cc/min and high flux filters of 800 cc/min) at a constant temperature of 37°C. The dialysis machine was initially calibrated weekly.

Table 1. Comparison of demographic/disease variables in control and intervention groups

Variable	Control group (n=37)	Intervention group (n=37)	Statistical tests
Age	57.16±13.81	55.86±13.56	P=0.68
Gender			
Female	20 (54.1)	20 (54.1)	P=1
Male	17 (45.9)	17 (45.9)	
History of taking sleeping pills			
Yes	8 (21.6)	7 (18.9)	P=0.77
No	29 (78.4)	30 (81.1)	
Taking L-Carnitine			
Yes	4 (10.8)	3 (8.1)	P=0.69
No	33 (89.2)	34 (91.9)	
Taking Erythropoietin			
Yes	32 (86.5)	26 (70.3)	P=0.09
No	5 (13.5)	11 (29.7)	
Mean BFV with high-flux filters	293.5±7.3	299.1±3.1	P<0.001
Mean BFV with low-flux filters	272.7±9.1	279.1±4.5	P<0.001
HD duration (month)	36.9±35.5	55.9±58.1	P=0.095
Pre-intervention DA	1.2±0.2	1.2±0.2	P=0.89
Post-intervention DA	1.2±0.1	1.3±0.1	P=0.001
BUN level after the 1st two sessions of HD before intervention	44.2±16.5	39.2±14.0	P=0.16
BUN level after 14th sessions of HD after intervention	46.3±14.5	38.1±11.1	P=0.008
Pre-intervention hemoglobin count	11.0±1.3	11.2±1.8	P=0.45
Post-intervention hemoglobin count	11.1±1.3	10.9±2.0	P=0.69

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran, (IR.MUMS.REC.1395.612) to conduct the study and make the necessary arrangements with 17-Shahrivar Hospital and Shafa Dialysis Center in Mashhad, Iran. Subsequently, the required permission and written informed consent were obtained from the authorities and the participants, respectively, to fulfill the ethical considerations in this study.

The data were analyzed in SPSS software (version 16) through independent t-test, repeated-measures ANOVA, Mann Whitney U test, and Chi-square test. In all tests, a p-value less than 0.05 was considered statistically significant.

Results

The mean±SD ages of the participants in control and intervention groups were 57.1±13.8 and 55.8±13.5 years, respectively. However, the independent t-test results showed no significant difference between these two groups in this respect (P=0.68). The Chi-square test results also demonstrated that the participants in both intervention and control groups were homogenous in terms of gender (P=1), as well as the history of taking sleeping pills (P=0.77), L-Carnitine (P=0.69), and Erythropoietin (P=0.09). Considering hemoglobin count before (P=0.45) and after (P=0.69) the intervention, there was no significant difference between the patients in this regard (Table 1).

Before the intervention, total fatigue mean±SD scores of the participants were 80.7±12.7 and 78.9±13.5 in the control and intervention groups, respectively. The Mann Whitney U test results similarly established no significant difference in terms of total mean scores of fatigue in the control and intervention groups at the pre-intervention stage (P=0.57).

In addition, the results of data analysis using repeated measures ANOVA indicated that the total fatigue mean scores of the participants in the intervention group had significantly reduced gradually

after being measured before the intervention, after the 8th session (i.e., two weeks), and after the 14th session (i.e., four weeks) (F=98.00, P≤0.001). The given test did also show a significant difference between the intervention and control groups in terms of the reduced level of fatigue (F=99.27, P≤0.001).
The results of repeated measures ANOVA also illustrated a significant and gradual decline in the fatigue mean score of the participants in the intervention group regarding the five dimensions of general, mental, and physical fatigue, as well as fatigue due to reduced activity and motivation before the intervention, and after the 8th (two weeks), as well as 14th sessions (four weeks) (P≤0.001).
Accordingly, there was a statistically significant difference between the intervention and control groups in terms of the reduced level of fatigue (P≤0.001) (Table 2).
In a similar vein, the results of the independent t-test indicated that the intervention group had significant improvements in DA after four weeks, compared to the pre-intervention stage (P=0.001) and the control group. On the other hand, the results of data analysis demonstrated no statistically significant difference between the control and intervention groups regarding the mean changes in BUN levels in the first two sessions before and after HD (P=0.16). However, the mean changes in BUN levels in the intervention group in the 14th session before and after HD were significantly different from those of the control group (P=0.008). In other words, BUN removal in the intervention group was higher than that in the control group.
Accordingly, Pearson's correlation coefficient showed a reverse but significant relationship between DA and fatigue in the study participants (P=0.032, r=0.250). In other words, improved DA could moderate fatigue, and there was also a direct relationship between BUN levels and fatigue (P=0.049, r=0.230). Accordingly, increased BUN removal led to a reduction in fatigue.

Table 2. Mean±SD scores of fatigue dimensions and total fatigue score in control and intervention groups

Variable	Control group Mean±SD	Intervention group Mean±SD	Repeated measures ANOVA
General fatigue after the 1st session of HD	16.1±2.5	16.0±3.0	Time effect
General fatigue after the 8th session	15.7±2.5	12.6±2.2	P≤0.001
General fatigue after the 14th session	16.1±3.0	8.7±2.5	Group effect P≤0.001
Physical fatigue after the 1st session of HD	17.4±3.2	17.3±3.0	Time effect
Physical fatigue after the 8th session	17.3±3.3	13.7±2.4	P≤0.001
Physical fatigue after the 14th session	18.0±3.3	10.3±2.2	Group effect P≤0.001
Mental fatigue after the 1st session of HD	14.6±3.6	13.8±.3.7	Time effect
Mental fatigue after the 8th session	14.4±3.4	10.5±3.2	P≤0.001
Mental fatigue after the 14th session	13.7±3.6	6.4±2.6	Group effect P≤0.001
Fatigue due to reduced activity after the 1st session of HD	17.86±3.1	17.7±3.2	Time effect P≤0.001
Fatigue due to reduced activity after the 8th session	17.7±3.0	14.5±5.6	Group effect P≤0.001
Fatigue due to reduced activity after the 14th session	18.0±2.8	10.6±2.6	
Fatigue due to reduced motivation after the 1st session of HD	14.62±2.91	14.10±3.06	Time effect P≤0.001
Fatigue due to reduced motivation after the 8th session	14.7±2.7	11.2±2.4	Group effect P≤0.001
Fatigue due to reduced motivation after the 14th session	14.9±2.6	8.0±2.5	
Total fatigue score after the 1st session of HD	80.7±12.7	78.9±13.5	Time effect
Total fatigue score after the 8th session	80.2±11.9	62.6±12.0	P≤0.001
Total fatigue score after the 14th session	80.8±12.9	44.1±9.7	Group effect P≤0.001

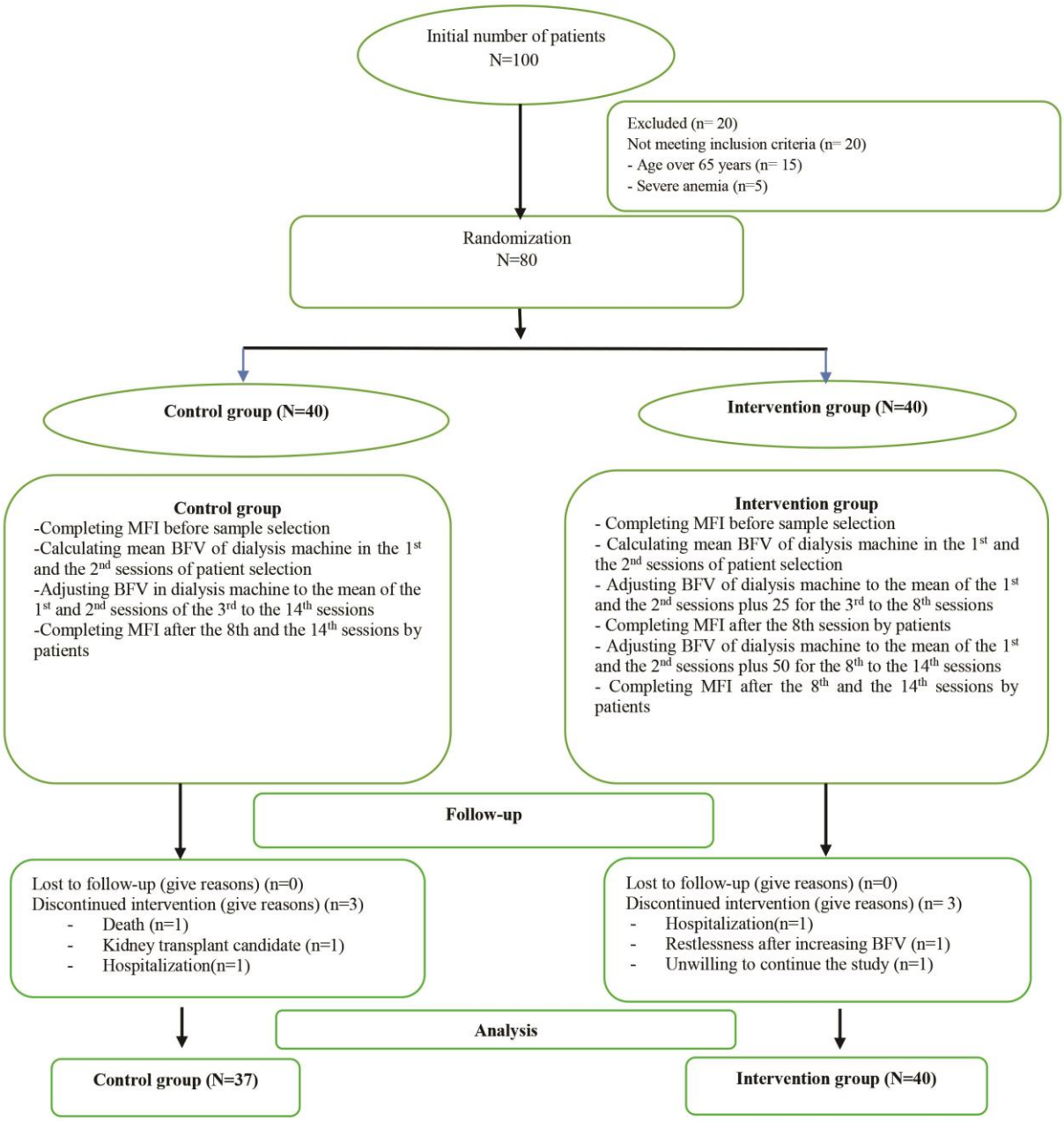

Figure 1. Workflow diagram

Discussion

The results of the present study showed that increased BFV of a dialysis machine could significantly and gradually reduce the fatigue mean scores of the participants in total and five dimensions of general, physical, and mental fatigue, as well as fatigue due to reduced activity and motivation during three times of measurement. Given that the BUN level is one of the physiological factors affecting fatigue in HD patients (17), the results of the present study showed that the participants in the intervention group had more BUN removal, compared to the control group. Therefore, higher levels of BUN removal leads to fewer levels of fatigue. On the other hand, considering the effective role of the BUN level in determining DA, the results established that the participants in the intervention group had better DA than that in the control group.

Reduced ability of the cardiovascular system to supply oxygen to the muscles and remove metabolism-induced products along with the accumulation of toxins, such as BUN can be the cause of fatigue in patients affected with CKD (17). Accordingly, this study hypothesized that if DA was increased by removing more waste, participants' fatigue would be diminished. The results of the

present study suggested that the high BFV of the dialysis machine led to better DA in the intervention group in a significant manner after 12 sessions of HD, compared to the control group. Moreover, the findings revealed an improvement in patients' fatigue during this time.

In line with the results of this study, Shahdadi et al. (2017) (20), Borzou et al. (2009) (18), and Gutzwiller et al. (2003) (21) had also reported in their studies that an increase in BFV would significantly enhance DA without intensifying HD complications (20). The blood pressure is a gold standard in hemodynamic conditions (31), and increased BFV did not reduce blood pressure in the present study. Moreover, Kim et al. (2004) stated that increased BFV by 15-20%, compared to the pre-intervention stage, resulted in improved DA, whereas the mean BUN removal was significantly increased in the participants (19).

However, none of the studies determined the relationship between fatigue in participants and changes in BFV during HD. Moreover, the results of the present study indicated a decline in fatigue levels among the participants throughout 12 sessions with a gradual rise in BFV in the dialysis machine. Therefore, the hypothesis of the present study confirmed the improvement of patients' fatigue with high BFV and improved DA. In addition to reducing fatigue, fatigue dimensions had also gradually diminished with an increase in the BFV in the dialysis machine.

In other words, general fatigue refers to a person's level of energy, a need for sleep and rest, getting tired early, and disturbance in a person's overall daily function in general (27). The results of the studies revealed that one-third of the patients undergoing HD were facing sleep problems, restless sleep, daily drowsiness (32, 33), and inadequate sleep, which probably led to insufficient performance and irritability. Therefore, there is the possibility that sleep disorders can create general fatigue (34). Considering the results of studies that showed improvements in sleep disorders and decreased severity of uremic pruritus following increased BFV of dialysis machine (24), the present study established that high BFV might boost a person's energy level by enhancing patients' sleep disorders, preventing premature fatigue, and possibly reducing patients' general fatigue.

Mental fatigue also represents cognitive symptoms in individuals, such as lack of concentration and distraction. This type of fatigue in HD patients can further lead to physical and mental weakness and inability to work, play roles, and perform tasks (27). It seems that increased BFV can boost concentration and reduce distraction, and ultimately mitigate mental fatigue through the removal of metabolic wastes.

The dimension of fatigue due to reduced activity also stands for problems in the patient's daily activities (27). Post-HD fatigue is thus a common debilitating symptom, which often occurs after HD sessions. This type of fatigue reduces activities, restricts patient's functions, and lowers social participation when this procedure is fulfilled (35). Increased BFV can also improve DA and enhance the patient's daily activities.

Additionally, the dimension of reduced motivation refers to a lack of motivation to initiate any activities (27). Accordingly, patients with CKD undergoing HD experience high levels of stress, anxiety, and depression. Dialysis often disables these patients and discourages them to engage in daily activities (36). These things make it impossible for a person to be motivated to do their daily activities. It seems that increased BFV generates a sense of energy by preventing the retention of waste products, thereby increasing motivation in HD patients.

In the present study, two-fold growth in BFV could lower fatigue more than twice that may be caused by increased BUN removal, removal of toxins from the body, and improved DA.

One of the limitations of this study was the small sample size. Therefore, larger sample size can help evaluate the more significant effects of increased BFV. Moreover, the individuals themselves could only evaluate the subjective nature of fatigue. Accordingly, the researchers' uncertainty of correctness and accuracy of the data and responses from the participants could be among the limitations of this study.

Implications for Practice

The results of the present study showed that a gradual increase in BFV of dialysis machines used for patients with CKD could significantly reduce fatigue in various dimensions by improving DA and boosting BUN removal. Moreover, an increase in the velocity of the dialysis machine can be easily performed by nurses working in dialysis departments. The BFV of dialysis machines can be increased to a maximum of 350 rpm concerning patient tolerance (patients' normal blood pressure) to reduce

their fatigue.

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Conflicts of Interest
The authors declared no conflict of interest regarding the publication of this study.

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