

# Disability and Rehabilitation

An international, multidisciplinary journal

<http://informahealthcare.com/dre>  
ISSN 0963-8288 print/ISSN 1464-5165 online

Disabil Rehabil, Early Online: 1–5  
© 2015 Informa UK Ltd. DOI: 10.3109/09638288.2015.1061601

**informa**  
healthcare

## RESEARCH PAPER

# The effects of an individual, multistep intervention on adherence to treatment in hemodialysis patients

Leila Rafiee Vardanjani<sup>1</sup>, Neda Parvin<sup>1</sup>, and Gholamreza Mahmoodi Shan<sup>2</sup>

<sup>1</sup>Department of Nursing, Shahrekord University of Medical Sciences, Shahrekord, Iran and <sup>2</sup>Department of Nursing, Golestan University of Medical Sciences, Golestan, Iran

### Abstract

**Purpose:** The present study was conducted to investigate the effect of individual, multistep intervention on adherence to treatment in hemodialysis patients referred to a hemodialysis center in Shahrekord, Iran.

**Method:** In this interventional study, hemodialysis patients referring the center of the study were randomly assigned into two control and intervention groups (each 33). The control group received routine treatment, recommended dietary and fluid restrictions. The intervention group participated in eight individual interventional sessions accompanied routine treatment. At the beginning and the end of the study, routine laboratory tests and end-stage renal disease-adherence questionnaire were filled out for patients in both groups. The data were analyzed using Mann–Whitney and Wilcoxon tests.

**Results:** At the end of the study, the two groups showed a significant difference in all domains of adherence except adherence to diet and adherence was better in the intervention group ( $p < 0.05$ ). In demographic characteristic, only age indicated a positive correlation with adherence to dialysis program ( $p = 0.04$ ,  $r = 0.254$ ). After intervention, serum phosphorus decreased significantly in the intervention group ( $p < 0.05$ ).

**Conclusions:** Adherence to treatment is one of the major problems in hemodialysis patients; however, comprehensive interventions are required in view of individual condition.

### Keywords

Adherence to treatment, hemodialysis, nurse

### History

Received 18 January 2015

Revised 26 May 2015

Accepted 9 June 2015

Published online 30 June 2015

### ► Implications for Rehabilitation

- Adherence to treatment means that all patients' behaviors (diet, fluids and drugs intake) should be in line with the recommendations given by healthcare professionals.
- There is evidence on the association between adherence to treatment and decreased risk of hospitalization in dialysis patients.
- Individual structured programs are most likely to be successful in encouraging adherence to treatment.

### Introduction

One of the common methods of treating the patients with end-stage renal disease (ESRD) is hemodialysis which causes change in lifestyle, health status and role of the individual [1,2]. These patients face numerous physical, psychological and social tensions [3]. One of the problems in hemodialysis patients is their adherence to treatment. Adherence to treatment means that all patients' behaviors (diet, fluids and drugs intake) should be in line with the recommendations given by healthcare professionals [4,5]. Adherence to diet, medication regimen and fluid restrictions are extremely important for the patients with chronic renal failure and could contribute strongly to improving health and feeling well in the patients under hemodialysis [4,6,7]. Today, there is evidence on the association between adherence to treatment and

decreased risk of hospitalization in dialysis patients. More than half of these patients believe that they do not follow therapeutic regimen, manifested by shortening dialysis duration, failing to take medications correctly, and observe dietary and fluid restrictions [8]. Meanwhile, failure to follow medication regimen is prevalent (about 25–86%) in hemodialysis patients [9], about 50% do not adhere to fluid restrictions and 44% in some aspects of diet [10]. Poor adherence in chronic renal failure patients often leads to additional tests, change in treatment design, change in prescribed drugs' dosage, hospitalization and finally increase in healthcare costs [11]. Nursing profession is committed to promote the patients' health using various interventions [12]. Different approaches and interventions such as face-to-face and video-assisted training [12], cognitive-behavioral technique [13] and self-efficiency training [14] have been adopted to enhance adherence in hemodialysis patients. Most of these approaches have been effective in only some domains of adherence. Lack of considering to individual conditions in hemodialysis patients seems to be one of the most important reasons for the patients'

Address for correspondence: Neda Parvin, Department of Nursing, Shahrekord University of Medical Sciences, Rahmatiee, Shahrekord, Iran. Tel/Fax: +98 3833335648. E-mail: np285@yahoo.com

non-adherence. The present study was conducted to determine the efficacy of an individual, multistep intervention on adherence to treatment and laboratory parameters in hemodialysis patients.

## Method

This interventional study was conducted through convenience random sampling between March 2013 and June 2013. The study protocol was approved by Ethics Committee of Gorgan University of Medical Sciences and registered as IRCT2012 091710857N1 in Iranian Registry of Clinical Trials. After obtaining informed consent for participation, the patients referring Hajar Hospital of Shahrekord with inclusion criteria enrolled in the study. The inclusion criteria were age over 18 years, ability to read and write, three dialysis sessions per week, at least 1-year dialysis history, ability to walk and eat independently, no mental or psychological and comorbid disease according to medical records, and interdialytic weight gain (IWG) higher than 2500 g and moderate or weak score of adherence to treatment according to end-stage renal disease-adherence questionnaire (ESRD-AQ). The patients who were unwilling to continue participation were excluded from the study. Two weeks before the beginning of the study, the patients were screened and those who had problems were identified. Finally, among 118 patients referring to the center of study, 66 patients were eligible. These patients were assigned randomly into both the intervention and control groups (each 33). The data were gathered at the beginning of the study and 1 week after last individual care session using a form consists of age, gender, marital status, level of education, economic status, dialysis duration, dry weight, average interdialytic weight gain, laboratory parameters and ESRD-AQ questionnaire [15] for both groups. The time of filling out the questionnaire was during the first hour of each hemodialysis session. Interdialytic weight gain was measured using the same digital scale (Pand, Pand Industries Co., Tehran, Iran) in the dialysis ward. The interdialytic weight gain above 2500 g meant failure to adhere to fluid restrictions [7,16,17].

*Validity and reliability of the instrument.* The ESRD-AQ questionnaire consists of 46 questions/items in five main domains of treatment adherence [15]. Initially, the questionnaire was translated into fluent Persian and then retranslated into English by a bilingual individual per forward and backward principles. Then, the two versions were compared with each other and no inconsistency was noted. To ensure face validity, the questionnaire was filled out by 10 literate patients. They were asked to identify the items difficult or vague for understanding. Then, the obtained questionnaire was reviewed quantitatively and qualitatively by 15 specialists on renal failure and dialysis-related disease and content validity index was calculated. The mean score of relevance, simplicity and clarity was obtained 99%, 98% and 97%, respectively. Overall content validity of the questionnaire was calculated 98%, which is acceptable. After the questionnaire was filled out by 10 patients within a 2-week interval based on test-retest, the reliability was estimated as 85%, which was acceptable.

*Scoring the questionnaire.* ESRD-AQ consists of five main domains: general information (5 items), adherence to hemodialysis treatment (14 items), adherence to drug treatment (9 items), adherence to fluid restrictions (10 items) and adherence to the recommended diet (8 items). The total adherence score was obtained by adding scores of the items below, maximally 1200 and minimally zero. The items 11, 12, 42, 41, 33, 32, 23 and 22 evaluate information and understanding of the patient about treatment adherence and the total score of this domain was obtained according to above items. High scores on this questionnaire represented better adherence, which were finally classified according to the Likert scale. As in Kim et al. study, one standard deviation higher and lower than mean adherence to the total

treatment and to different treatment domains was defined as moderate adherence, the scores lower than moderate were considered as weak and those higher than moderate as good [15].

*Intervention.* The patients in control group underwent hemodialysis, routine recommended dietary and fluid restrictions, and pharmacotherapy. While, in the intervention group, multistep individual intervention was implemented in addition to the intervention conducted for the control group. For the patients in the intervention group, eight individual sessions (each session 1-h) were conducted by researchers (a critical care nurse and a psychiatric nurse), while the patient was under hemodialysis [18].

## Description of sessions

The intervention in each study group was performed in specific shifts and days (in the morning shifts and even days for patients in the intervention group and other shifts and odd days for the control group), therefore there was no overhearing the intervention for patients in the control group.

*First session:* In this session, after getting more familiar with the patient, researcher explained the purposes of the study and examined the level of the patient's information on dietary and fluid restrictions, medication regimen and the importance of dialysis treatment continuation.

*The second and third sessions:* Within these sessions, regarding the results of the first session, researcher planned for each individual. In these sessions general information about chronic renal failure and the need for dialysis, normal level of routine laboratory tests, nutritive value of the food and the amount of dietary and fluid restrictions in renal failure, importance of treatment continuation and general hemodialysis mechanism as an artificial kidney was given to the patients.

*The fourth and fifth sessions:* In these sessions, according to the results of previous sessions, in each domain with lack of adherence, some recommendations were given to each patient.

*The sixth and seventh sessions:* In these sessions, based on the activities performed in previous sessions, the researcher discussed about the patient's adherence status and the learned skills. In addition, patients with good adherence between the sessions were encouraged.

*Eighth session:* In addition to concluding the sessions, an opportunity for questioning and answering was provided for the patients and their information was completed throughout this session. Finally, 1 week after this session, the end evaluation was conducted by the ESRD-AQ questionnaire. The obtained data were analyzed using SPSS 16.0 software (SPSS Inc., Chicago, IL). Shapiro–Wilk test indicated that the data were not normal in view of different subscales and the total score of adherence ( $p < 0.05$ ). Statistic tests such as Pearson's correlation coefficient, chi-square, Mann–Whitney and Wilcoxon were used for data analysis.

## Results

Among 118 patients referring to the center of the study, 35 were older than 75 years old, 8 patients had mental retardation or unable to communicate due to blindness or deafness, so 43 patients were excluded from the study. In the remaining patients, four were not willing to participate in the study. Finally, after completion of ESRD-AQ, five patients (7.04%) had a good level of adherence and were excluded from the study. The remaining 66 patients were randomly assigned into both the intervention ( $n = 33$ ) and control ( $n = 33$ ) groups (Figure 1). The mean age of the intervention and control groups were 53.97 SD 15.7 and 53.36 SD 14.9 years, respectively. The mean age of dialysis in the intervention group was 4.6 SD 4.7 years and in the control 5.74 SD 3.9. In neither of the above characteristics, nor statistically

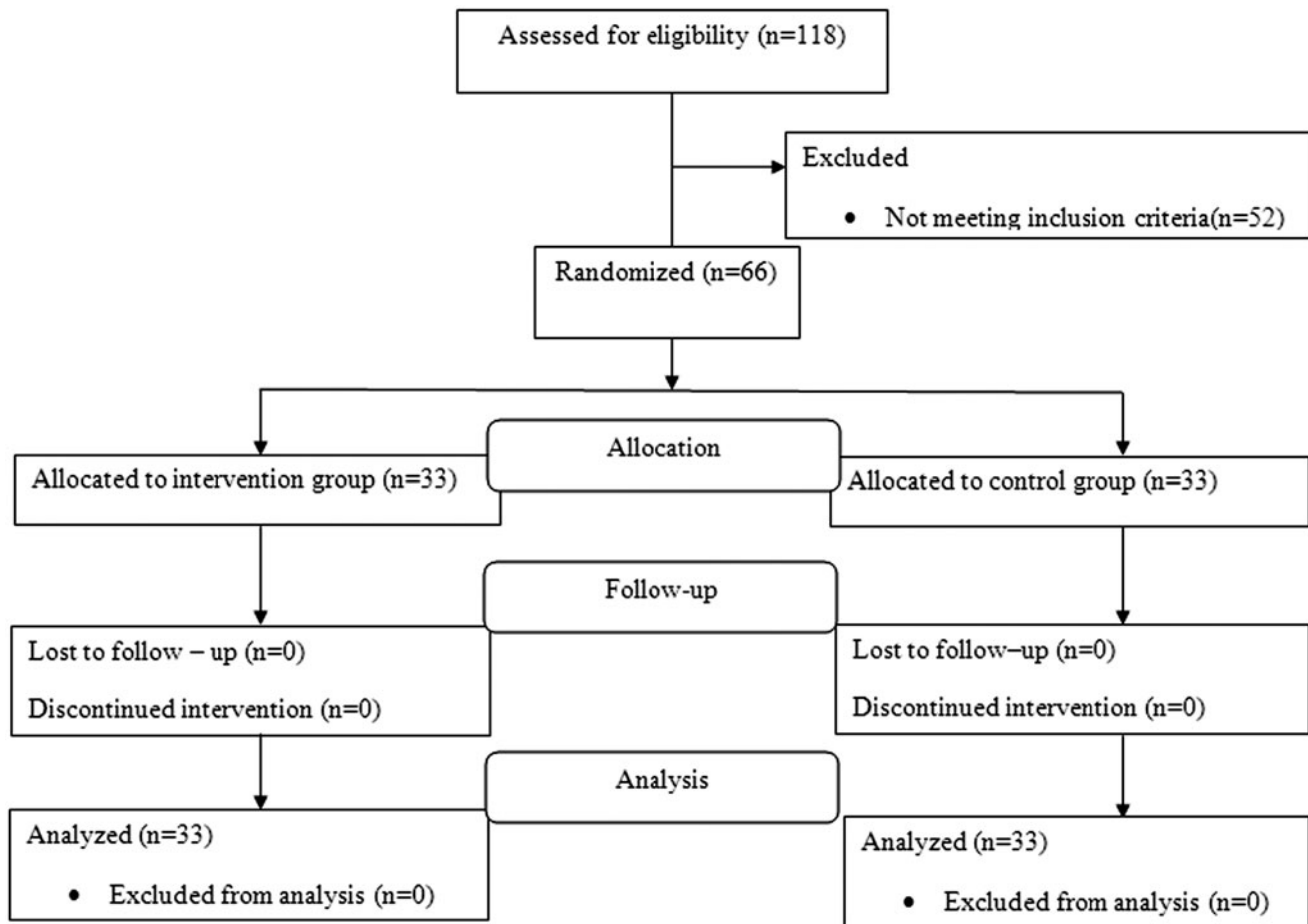


Figure 1. Enrolment stage.

Table 1. Laboratory parameters at the beginning and the end of the study in two groups.

Laboratory parameters	Beginning stage			End stage		
	Intervention group	Control group	<i>p</i> Value	Intervention group	Control group	<i>p</i> Value
Hemoglobin (g/dl)	10.16 SD 1.79	10.77 SD 1.61	0.2	10.67 SD 1.16	10.73 SD 1.38	0.52
Sodium (meq/l)	141.42 SD 4	142 SD 3.69	0.68	141.45 SD 4.02	141.77 SD 3.85	0.73
Potassium (meq/l)	4.9 SD 0.56	5 SD 0.55	0.35	4.9 SD 0.53	4.96 SD 0.54	0.33
Phosphor (mg/dl)	4.99 SD 0.9	5.19 SD 1.55	0.47	4.67 SD 0.53	4.91 SD 0.85	0.006
Creatinine (mg/dl)	6.46 SD 1.88	6.25 SD 1.61	0.66	6.03 SD 1.73	6.13 SD 1.65	0.47
BUN (mg/dl)	70 SD 21.12	68.72 SD 23.02	0.8	61.18 SD 25.04	dl 65.06 SD 23.96	0.11
Calcium (mg/dl)	8.93 SD 0.22	8.89 SD 0.69	0.3	8.99 SD 0.34	8.92 SD 0.53	0.75
Albumin (g/dl)	5.04 SD 0.73	5.06 SD 0.62	0.7	5.05 SD 0.73	5.03 SD 0.68	0.96
Alkaline phosphatase (μl)	324.39 SD 200.5	369.24 SD 419	0.76	313.79 SD 206.39	340.86 SD 329.14	0.54

significant difference was observed between both groups ( $p > 0.05$ ). In addition, chi-square indicated that the two groups had no significant difference in gender ( $p = 0.06$ ), marital status ( $p = 0.255$ ), educational level ( $p = 0.102$ ), income ( $p = 0.45$ ) and cause of development renal failure ( $p = 0.832$ ). Also, the two groups had no significant difference in laboratory parameters ( $p > 0.05$ ). Wilcoxon test indicated no significant difference in laboratory parameters before and after the study in the control group, while in the intervention group, hemoglobin ( $p = 0.008$ ), phosphorus ( $p = 0.005$ ), creatinine ( $p = 0.04$ ) and blood urea nitrogen (BUN) ( $p = 0.01$ ) had a significant difference between the two stages, with better conditions at the end of the

study (Table 1). In addition, at the end of the intervention, only phosphorus level had a significant difference between the two groups. Other laboratory parameters were not significantly different between the two groups ( $p > 0.05$ ).

Mann-Whitney test showed that there were no significant differences in four main domains and total adherence score at the beginning of the study in two groups ( $p > 0.05$ ). After the intervention, all domains except adherence to diet were significantly better in the intervention group than the control, showing the efficacy of intervention (Table 2). At the beginning of the study, the mean dry weight of the patients was 64.33 SD 14.22 kg in the intervention group and 63.07 SD 13.79 in the

Table 2. Adherence to treatment at the beginning and the end of the study in two groups.

Adherence domain	Beginning stage			End stage		
	Intervention group	Control group	<i>p</i> Value	Intervention group	Control group	<i>p</i> Value
Adherence to drug treatment	128.78 SD 73.98	139.39 SD 51.71	0.17	175.75 SD 33.35	133.33 SD 64.54	0.003
Adherence to fluid restrictions	110.6 SD 55.56	119.69 SD 49.9	0.51	163.63 ± 56.28	136.36 SD 60.3	0.02
Adherence to the recommended diet	101.51 SD 64.32	101.51 SD 53.74	0.7	100 SD 62.5	96.96 SD 58.54	0.67
Adherence to hemodialysis treatment	471.24 SD 122.46	512.15 SD 122.93	0.14	596.21 SD 17.81	478.78 SD 71.29	<0.001
Total of adherence	812.15 SD 189.16	872.75 SD 180.41	0.09	1035.6 SD 88.6	846.97 SD 138.31	<0.001

control ( $p < 0.05$ ). The mean interdialytic weight gain was 3457.6 SD 1549.6 g in the intervention group and 3227.3 SD 899.05 in the control ( $p < 0.001$ ).

## Discussion

The finding of the study indicated that this intervention was effective on improvement of treatment adherence in hemodialysis patients. In the intervention group, interdialytic weight gain at the end of the study was lower compared to the control group; therefore, the intervention has been effective. This result is similar with findings of Tsay et al. [14], Rambod et al. [19] and Shomali [20]. Interdialytic weight loss seems to be due to the effect of the training on blood sugar control, ice usage, less exposure to heat, doing activities in cooler hours of the day and increase in patients' awareness of adherence to fluid restriction. In this study, intervention was effective only in phosphorus level, similar to study of Shaw-Stuart et al. which concluded that training programs can decrease serum phosphate levels [21]. However, in some studies, intervention was improved the other laboratory parameters. In Rambod et al. study [19], all laboratory parameters improved after intervention in the intervention group. The inconsistency in findings is probably related to different factors such as inadequate dialysis time, shortness of intervention and difficulty of adherence to diet. In present study, no significant association was observed between demographic variables and adherence domains except age and adherence to dialysis program, while in Barnett et al. study, no statistically significant associations were detected between interdialytic weight gain, age, educational level, marital and employment status. In addition, women demonstrated a greater decrease in mean interdialytic weight gain than men [22]. In present study, interdialytic weight gain in younger individuals was higher than the older similar to Mellon study, that only age was associated with adherence [23]. Park in his study concluded that older hemodialysis patients had a lower awareness, less appetite and were at a higher risk of death compared to the younger. Park believed that the training programs should be planned appropriate to older patients, with emphasizing the increase in their awareness of diet and nutrition [24]. Most of patients in this study took cardiac drugs and phosphate binders, which is in agreement with García-Llana [25] and Karamanidou et al. [26] studies.

Lack of adherence to medication regimen in dialysis patients is probably due to complexity, numerous medications, lack of organized training to patients about importance of properly drugs' taking and how to take them, and finally drugs' side-effects, particularly gastrointestinal difficulties such as gastric pain. These problems decreased in the intervention group through individual strategies like special dishes for drug division, suggesting appropriate time for dividing and taking drug, emphasizing the necessity of taking drugs and their importance in the treatment course. In Neri study therapeutic regimen was very weak and complexity of medication regimen was one of the reasons for this issue, which improved after training [18]. In this study, individual

intervention caused improvement of adherence to fluid restrictions in the intervention group. In the study center, there was no organized training on fluid restrictions and most patients had difficulty adhering to fluid restriction. Inadequate knowledge on importance of daily weighing was one of the potential reasons for lack of adherence to fluid restrictions. During the study, different behavioral approaches, like training saying no and thought distraction, were used to control the patient's behavior. Moreover, the patients were encourage for blood sugar control, sugar-free chewing gum, ice usage, less exposure to heat and doing activity during cooler hours of the day. Effectiveness of the interventions on adherence to fluid restrictions has been obtained consistently in different studies. In Hegel et al. study, behavioral treatments had short-term effects on adherence to fluid restrictions [27]. Tsay et al. [14] also demonstrated the efficacy of training on adherence to fluid restriction. In this study, adherence to dialysis program improved in the intervention group, while no change was observed in the control group. It seems that lack of training on significance of dialysis treatment continuation, difficulty of adherence to dialysis program, commuting and other job-related issues at the time of dialysis session are the main reasons for missing dialysis sessions. During the study, regarding the patients' difficulties, the researcher concentrated on developing a dialysis program in view of occupational conditions and promotion of awareness about dialysis program importance and altered it, as much as possible, according to their living and occupational conditions.

At the end of the study, the two groups had no significant difference in adherence to diet. Inadequate awareness and economic problems caused the food consumed by the patients to be restricted to specific items. The majority of the patients in this study had a poor economic status and obviously, inability to provide suitable food could not be removed only by training and expressing the significance of adherence to dietary restrictions. Therefore, the offered training on this aspect of intervention was not effective. In contrast to this study, Hassanzadeh et al. in their study indicated that face-to-face and video-assisted training was effective on the patients' diet status [12]. This inconsistency is possibly attributable to different cultural, economic, financial and climatic conditions of the patients under the two studies. The total adherence score in the intervention group improved significantly compared to the control group, consistent with the results of Tanner et al. study [28].

## Conclusion

Overall, the existing inconsistency in the findings of the studies on adherence to treatment could be explained by economic status, deprivation and living conditions in study regions, and the patients' extra fees like commuting for dialysis, lack of efficient employment, comorbid diseases and different methods of adherence assessment tools. In view of low number of the hemodialysis patients referring the center of this study, other study with a larger sample size in different hemodialysis centers is recommended.



### Limitation of study

In present study, patients in the intervention group received not only attention but also individual educational program regarding to their questionnaires. However, the effect of attention or individual intervention is indiscernible and need to complementary study. The other limitation of the present study is that there are no long-term outcomes that the intervention effect may be lost with time as there was not follow-up for six months post-intervention.

### Acknowledgements

The authors thank the nursing staff and hemodialysis patients of Hajar Hospital, Shahrekord, Iran.

### Declaration of interest

The authors report no declarations of interest. This study was financed by Golestan University of Medical Sciences. This article was obtained from a nursing MSc thesis approved at Golestan University of Medical Sciences (ethics code: 356191122721) and funded by Research and Technology Deputy of this university.

### References

1. Kaba E, Bellou P, Iordanou P, et al. Problems experienced by haemodialysis patients in Greece. *Br J Nurs* 2007;16:868–72.
2. Al-Arabi S. Quality of life: subjective descriptions of challenges to patients with end stage renal disease. *Nephrol Nurs J* 2006;33:285–92.
3. Thomas-Hawkins C. Symptom distress and day-to-day changes in functional status in chronic hemodialysis patients. *Nephrol Nurs J* 2000;27:369–79.
4. Takaki J, Yano E. Possible gender differences in the relationships of self-efficacy and the internal locus of control with compliance in hemodialysis patients. *Behav Med* 2006;32:5–11.
5. Kaveh K, Kimmel PL. Compliance in hemodialysis patients: multidimensional measures in search of a gold standard. *Am J Kidney Dis* 2001;37:244–66.
6. Takaki J, Nishi T, Shimoyama H, et al. Possible variances of blood urea nitrogen, serum potassium and phosphorus levels and interdialytic weight gain accounted for compliance of hemodialysis patients. *J Psychosom Res* 2003;55:525–9.
7. Denhaerynck K, Manhaeve D, Dobbels F, et al. Prevalence and consequences of nonadherence to hemodialysis regimens. *Am J Crit Care* 2007;16:222–35.
8. Vaiciuniene R, Kuzminskis V, Ziginiskiene E, et al. Adherence to treatment and hospitalization risk in hemodialysis patients. *J Nephrol* 2012;25:672–8.
9. Gerbino G, Dimonte V, Albasi C, et al. Adherence to therapy in patients on hemodialysis. *G Ital Nefrol* 2011;28:416–24.
10. Khalil AA, Frazier SK, Lennie TA, Sawaya BP. Depressive symptoms and dietary adherence in patients with end stage renal disease. *J Renal Care* 2011;37:30–9.
11. Loghman-Adham M. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. *Am J Manag Care* 2003;9:155–71.
12. Hasanzadeh F, Shamsoddini S, Moonaghi HK, Ebrahimzadeh S. A comparison of face to face and video-based education on attitude related to diet and fluids adherence in hemodialysis patients. *Ofohge-Danesh J* 2011;17:34–43.
13. Lindberg M, Wikström B, Lindberg P. A behavioural nursing intervention for reduced fluid overload in haemodialysis patients. Initial results of acceptability, feasibility and efficacy. *J Nurs Healthcare Chronic Illn* 2011;3:87–98.
14. Tsay SL. Self-efficacy training for patients with end-stage renal disease. *J Adv Nurs* 2003;43:370–5.
15. Kim Y, Evangelista LS, Phillips LR, et al. The End-Stage Renal Disease Adherence Questionnaire (ESRD-AQ): testing the psychometric properties in patients receiving in-center hemodialysis. *Nephrol Nurs J* 2010;37:377–93.
16. Bame SI, Petersen N, Wray NP. Variation in hemodialysis patient compliance according to demographic characteristics. *Soc Sci Med* (1982) 1993;37:1035–43.
17. Sezer S, Ozdemir FN, Arat Z, et al. The association of interdialytic weight gain with nutritional parameters and mortality risk in hemodialysis patients. *Renal Fail* 2002;24:37–48.
18. Neri L, Martini A, Andreucci VE, et al. Regimen complexity and prescription adherence in dialysis patients. *Am J Nephrol* 2011;34:71–6.
19. Rambod M, Peyrovi H, Sareban M. Relationship of self-efficacy with therapeutic regimen and clinical/laboratory outcomes in hemodialysis patient. *Iran J Nurs* 2010;22:41–7.
20. Shomali M. Effect of education boeed on educational needs on weight changes in patients undergoing haemodialysis. *Nurs Midwifery Care J* 2012;2:25–33.
21. Shaw-Stuart NJ, Stuart A. The effect of an educational patient compliance program on serum phosphate levels in patients receiving hemodialysis. *J Renal Nutr* 2000;10:80–4.
22. Barnett T, Li Yoong T, Pinikahana J, Si Yen T. Fluid compliance among patients having haemodialysis: can an educational programme make a difference? *J Adv Nurs* 2008;61:300–6.
23. Mellon L, Regan D, Curtis R. Factors influencing adherence among Irish haemodialysis patients. *Patient Educ Couns* 2013;92:88–93.
24. Park K, Choi-Kwon S, Sim YM, Kim SB. Comparison of dietary compliance and dietary knowledge between older and younger Korean hemodialysis patients. *J Renal Nutr* 2008;18:415–23.
25. García-Llana H, Remor E, Selgas R. Adherence to treatment, emotional state and quality of life in patients with end-stage renal disease undergoing dialysis. *Psicothema* 2013;25:79–86.
26. Karamanidou C, Clatworthy J, Weinman J, Horne R. A systematic review of the prevalence and determinants of nonadherence to phosphate binding medication in patients with end-stage renal disease. *BMC Nephrol* 2008;9:2.
27. Hegel MT, Ayllon T, Thiel G, Oulton B. Improving adherence to fluid restrictions in male hemodialysis patients: a comparison of cognitive and behavioral approaches. *Health Psychol* 1992;11:324–30.
28. Tanner JL, Craig CB, Bartolucci AA, et al. The effect of a selfmonitoring tool on self-efficacy, health beliefs, and adherence in patients receiving hemodialysis. *J Renal Nutr* 1998;8:203–11.