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ORIGINAL ARTICLE

Effect of Protein Supplementation on Serum Electrolytes in Hemodialysis Patients

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ABSTRACT

Background: Controlling malnutrition in hemodialysis (HD) patients is of great concern. On the other hand, managing serum electrolytes including calcium, phosphorus, sodium, and potassium at the same time is critical to improve patients' survival. The aim of this study was to evaluate the effect of whey protein supplementation on serum electrolytes in HD patients.

Methods: Ninety two 17 to 65 years old HD patients were randomly assigned to four groups of (i) receiving whey beverage fortified with vitamin E, (ii) receiving whey beverage, (iii) receiving vitamin E, and (iv) as the control group receiving no intervention (for 8 weeks). At the beginning and at the end of the study phase, serum electrolytes including serum calcium, phosphorus, potassium, and sodium were measured using the automated techniques.

Results: After comparing all groups, it was demonstrated that there were significant decreases in serum phosphorus in group 1 and group 2, that both were significantly different from the control group. On the other hand, in group 3, serum potassium reduced afterintervention, which was significantly different form the control group. Serum sodium significantly decreased in group 2 in comparison to control group.

Conclusion: Whey beverage fortified with vitamin E didnot disturb HD patients' serum electrolytes and helped HD patients to improve and control serum electrolytes. This warrants more investigations to find the exact mechanisms of the effects of whey or vitamin E on serum electrolytes.

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Introduction

End-stage renal disease (ESRD), as a condition of renal failure, is accompanied by various complications including uremia (1), malnutrition (2-4), mineral, electrolyte, and bone disorders (5). Controlling clinical complications in ESRD patients, especially HD patients, is of great concern. So controlling malnutrition is an important factor in HD patients as it is the main reason for hospitalization and mortality in HD patients. On the other hand, regarding electrolyte imbalance in HD patients, it's of great importance to manage serum electrolytes including phosphate and calcium in HD patients simultaneously (5).

High serum calcium is associated with vascular calcification in ESRD patients that might threaten their survival. In addition, hyper-phosphatemia can also cause vascular calcification and is associated

with cardiovascular events and mortality in patients on maintenance dialysis (6-8). As it is always mentioned, cardiovascular events are the main reasons for morbidity and mortality in ESRD and HD patients (3). Hence, serum phosphate and calcium levels should be kept within the normal range in pre-dialysis and HD patients (9, 10).

Another electrolyte with important features in HD patients is potassium. It is a concern that any change in serum potassium might cause cardiac fatal outcomes. For instance, hyperkalemia might induce fatal arrhythmia in HD patients (11). Preventing serum potassium disturbances or fluctuations is possible through effective HD or dietary therapy and in this way, deaths due to hyperkalemia in this population can be avoided (12). Moreover, low sodium content in the body or serum, can reduce fluid overload and hypertension, and in this way, it can diminish cardiovascular mortality in HD patients (13).

As it was mentioned, managing malnutrition in HD patients is of great importance, and this can be done by protein supplements. But, of course, it is critical to control serum electrolytes at the same time. One of the recommended proteins in improving nutritional status in HD patients is whey protein. It has a low content of phosphorus, sodium, and potassium. So, it might be a safe protein for HD patients, but as we are not sure about its effects on serum electrolytes in this population.Therefore, this study was undertaken to evaluate the effects of oral protein supplementation (whey protein), in the form of a beverage on serum electrolytes in HD patients.

Materials and Methods

This study was a randomized controlled parallel trial that was approved by Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran and conformed to the Declaration of Helsiniki and Good Practice Guidelines. Inclusion criteria included age of 17 to 65 years old, being under regular hemodialysis in hemodialysis centers of Shiraz University of Medical Sciences, Shiraz, Iranmaking them eligible for participation in this study. Exclusion criteria were those taking antioxidant supplements, amino acids, protein or keto-acid supplements, or immunosuppressive medications within the 2 months prior to recruitment in the study, or having active infection or hospitalization in the previous month.

Malnourished patients (mild, moderate, or severe) according to subjective global assessment (SGA) scoring were included in this study.A number of 300 patients were screened and almost 92 of them were eligible and they signed the informed consent to participate in this trial. Patients were recruited by referral to the specified HD center. The eligible patients were dialyzed with polysulfone/polyamide membranes, reverse osmosis purified water and bicarbonate containing dialysate.

By using balanced block randomization, we divided the patients into 4 groups. The patients in the first group received 3 bottles of fermented whey beverage fortified with vitamin E per week for 8 weeks (each bottle: 220 mL, 15 g WPC+600IU vitamin E (all-rac-α-tocopherol). Those in the second group received 3 bottles of fermented whey beverage per week for 8 weeks (each bottle: 220 mL, 15 g WPC: substituted the animal protein in the diet), and those in the third group received three capsules of vitamin E per week in the form of all-rac-α-tocopherol for 8 weeks (600 IU vitamin E). For the control group, the patients received no intervention and just usual care and nutritional consultation were provided to them.

The beverages were processed by Ramak Dairy Company in prepackaged bottles numbered for each patient based on the randomization sequence. The vitamin E dose was determined according to previous investigations for HD patients (14). On the other hand, 15 grams of whey protein were used for processing beverages. This amount of protein as a low phosphorus (9.35 mg/100 g), low sodium (62.5 mg/100 g), and low potassium (0.0295%) source, was used to replace animal protein in diets. We visited each patient on dialysis sessions for evaluating their compliance. For laboratory measurements, blood samples were taken from each patient just before the onset of the HD session at the beginning and at the end of the study. After centrifugation, the serum was separated and stored. Serum levels of electrolytes including calcium, phosphorus, sodium, and potassium were measured at the baseline and at the end of the study using automated techniques.

Statistical analysis was done using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Paired-t test was used for assessing changes in each group during the treatment phase for normally distributed data and Wilcoxon's signed-rank test for the skewed data. For comparing the changes in serum electrolytes among 4 groups, analysis of covariance (ANCOVA) model with treatment as the main effect and the baseline parameters as covariates was used. Bonferroni post-hoc test was performed to assess pair-wise differences between the groups to adequately adjust for multiple comparisons. For the skewed data, a logarithmic correction was performed before analyzing. A p value of <0.05 was considered statistically significant.

Results

The patients were between the ages of 17 and 65 years. Forty women and 52 men participated in the study. The mean age and number of women and men participating in each study group were presented separately in Table 1. A total of 9 patients were excluded from different groups for different reasons (non-cooperation or kidney transplantation; 2 patients from whey beverage fortified with vitamin E group, 3 from whey beverage group, 1 from the vitamin E group and 3 from the control group). All of the investigated markers did not have a significant difference between the groups at the beginning of the study, and in this regard, the groups were relatively similar (Table 1).

Regarding changes in serum electrolytes, the results indicated that there was no significant change in serum calcium level in the studied groups during the two month period (Tables 2, 3, and 4) and there was no significant difference between the groups (Table 5). However, there was a significant decrease in serum phosphorus levels in whey beverageand whey beverage fortified with vitamin E groups (P=0.001 and P=0.002, respectively; Tables 2 and 3).

Table 1: Demographic characteristics and basic parameters measured in the patients

Variable	Group				P value
	Control (n=23)	Vitamin E (n=23)	Whey beverage (n=23)	Whey beverage fortified with vitamin E (n=23)	
Age (year)	55±6.5	58±8.7	57±9.6	56±9.1	-
Sex (men/women)	10 (13)	13 (10)	10 (13)	14 (9)	-
BUN*(mmol/l)	122.13±52.87	112.48±23.77	120.3±25.14	122.43±28.63	0.74
Creatinine* (mg/dl)	8.11±3.14	7.87±2.99	8.3±2.1	8.68±2.34	0.79
Sodium* (meq/l)	137.21±4.29	137.33±4.34	139.18±3.7	138.04±2.87	0.32
Potassium* (meq/l)	5.92±0.8	5.76±0.95	5.52±0.81	5.65±0.85	0.49
Calcium*(mg/dl)	8±0.61	7.79±0.55	8.49±0.72	8.8±0.66	0.65
Phosphorus*(mg/dl)	4.82±1.23	4.55±1.21	4.82±0.92	5±0.7	0.53

*Mean±standard deviation,In order to compare the bases between the four groups, ANOVA was used for normal data.#To compare the mean values between the four groups, Kruskal-Wallis test was used for data with abnormal distribution

Table 2: Comparison of measured indices in whey beverage fortified with vitamin E group before and after the intervention

Variable	After intervention		Before intervention		P value*
	Mean	Standard deviation	Mean	Standard deviation	
BUN (mmol/L)	108.52	34.57	122.43	28.62	0.003
Creatinine (mg/dL)	7.64	2.54	8.68	2.34	0.00
Calcium (mg/dL)	8.87	0.84	8.8	0.66	0.91
Phosphorus (mg/dL)	4.43	0.99	5	0.7	0.001
Sodium (meq/L)	135.18	4.56	138.04	2.87	0.018
Potassium (meq/L)	5.53	0.56	5.65	0.85	0.45

*Significant at Pvalue<0.05 (Comparison of baseline and two-month parameters were performed by Paired t-test for normal data). #To compare base and two-month parameters for data with abnormal distribution, Wilcoxon signed rank test was used

Table 3: Comparison of measured indices in whey beverage group before and after the intervention

Variable	After intervention		Before intervention		P value
	Mean	Standard deviation	Mean	Standard deviation	
BUN (mmol/L)	110.55	19.89	120.3	25.14	0.006
Creatinine (mg/dL)	7.47	2	8.3	1.2	0.001
Calcium (mg/dL)	8.38	0.78	8.49	0.72	0.30
Phosphorus (mg/dL)	4.24	0.78	4.82	0.92	0.002
Sodium (meq/L)	135.38	3.53	139.18	3.77	0.00
Potassium (meq/L)	5.2	0.75	5.52	0.81	0.06

*Significant at P value<0.05 (Comparison of baseline and two-month parameters were performed by Paired t-test for normal data). #To compare base and two- month parameters for data with abnormal distribution, Wilcoxon signed rank test was used

While a significant increase was observed in the serum phosphorus levels in the control group during the two-month period (P=0.017, Table 4), the observed changes in the vitamin E group during this period were not significant (Table 4). On the other hand, in assessing the changes and comparing serum phosphorus levels between groups, the results showed that there was a significant difference between the groups (P<0.001). This difference mainly refers to the observed difference between whey beverage fortified with vitamin E group with control Group, and whey beverage group with the control group (Table 5).

In terms of serum potassium changes, the results for the 2-month period indicated that although there was an increase in the control group and a decrease in the treatment groups, the changes observed in any of the groups were not significant. Only in the vitamin E group, there was a significant decrease in serum potassium levels (P=0.034, Table 4).But, in general, there was a significant difference between the groups in comparison to the changes between the groups (P=0.009, Table 5). This resulted from the observed difference between the group vitamin E and control, as well as whey beverageand control group.

In addition, in the study of serum sodium levels, the results indicated a significant decrease in serum sodium levels in the group of whey beverage fortified with vitamin E (P=0.018) and in the whey beverage group (P<0.001) during the two month period (Tables 2 and 3). However, changes in serum sodium levels observed in the group vitamin E and control were not significant, during the study period (Table 4).On the other hand, there was a significant difference between the observed changes among the four groups during the course of study (P=0.01, Table 5), which is mainly due to the difference between the group whey beverage and the control group.

Table 4: Comparison of measured indices in vitamin E and control groups before and after the intervention

Groups	Variable	After intervention		Before intervention		P value
		Mean	Standard Deviation	Mean	Standard Deviation	
Vitamin E group	BUN (mmol/L)	118.05	30.33	112.48	23.77	0.06
	Creatinine (mg/d L)	7.59	2.74	7.87	2.99	0.41
	Calcium (mg/d L)	7.92	0.63	7.79	0.55	0.19
	Phosphorus (mg/d L)	4.49	1.26	4.55	1.21	0.92
	Sodium (meq/ L)	135.11	2.72	137.33	4.34	0.05
	Potassium (meq/ L)	5.31	0.78	5.77	0.95	0.03
Control group	BUN (mmol/L)	139.55	50.84	122.13	52.87	0.04
	Creatinine (mg/d L)	8.93	3.82	8.11	3.14	0.03
	Calcium (mg/d L)	7.6	1.25	8	0.61	0.197
	Phosphorus (mg/d L)	5.21	1.24	4.82	1.23	0.017
	Sodium (meq/ L)	137.78	4.36	137.21	4.29	0.445
	Potassium (meq/ L)	4.06	0.95	5.92	0.80	0.053

*Significant at P value<0.05 (Comparison of baseline and two-month parameters were performed by Paired t-test for normal data). #To compare base and two-month parameters for data with abnormal distribution, Wilcoxon signed rank test was used.

Table 5: In-group and intra-groups comparison of measured indices over a two month period

Variable	*P inter-groups	#P intra-groups
BUN (mmol/L)	Groups 1 and 3: 0.029	0.001
	Groups 1 and 4: 0.00	
	Groups 2 and 3: 0.42	
	Groups 2 and 4: 0.001	
Creatinine (mg/dL)	Groups 1 and 4: 0.00	0.001
	Groups 2 and 4: 0.00	
	Groups 3 and 4: 0.04	
Calcium (mg/dL)	Not significant	0.17
Phosphorus (mg/dL)	Groups 1 and 4: 0.001	<0.001
	Groups 2 and 4: 0.002	
Sodium (meq/L)	Groups 2 and 4: 0.008	0.01
Potassium (meq/L)	Groups 2 and 4: 0.046	0.009
	Groups 3 and 4: 0.007	

#To compare the groups together, ANOVA test was used for normal data and for abnormal data Kruskal Wallis was used (IL-6 and HDL). *Obtained from Bonferroni post-hoc. Group 1: Whey beverage fortified with vitamin E, Group 2: Whey beverage, Group 3: Vitamin E, Group 4: Control

Discussion

In the present study, the effects of whey beverage and whey beverage fortified with vitamin E as an antioxidant (14) on serum electrolytes were studied. The results of this study indicated the improvementeffects of whey beverage in both enriched or non-enriched forms, on serum phosphorus levels and its reduction. However, in the control group, an increasing trend has been observed in serum phosphorus levels. These results showed a significant difference between whey beverage groups with the control group. Possibly, the main reason for the observed effect is the low content of phosphorus in these beverages.

Since these beverages are a substitute for the dietary protein intake, the use of a low protein phosphorus source may have a potential effect on the reduction of serum phosphorus levels relative to animal protein sources that are rich in phosphorus. Also, because high serum phosphorus levels in hemodialysis patients are the main causes of increased risk of hospitalization and mortality (6-8, 15), any decrease in serum phosphorus levels, might have a positive effect on the health of these patients and whey beverage can be accompanied by a reduction in serum phosphorus level with beneficial health outcomes.

Meanwhile, no study has not been conducted on the effects of this protein on the serum phosphorus levels in hemodialysis patients. Therefore, this protein is not only safe in terms of serum phosphorus levels, but also, it helps to control the serum level in hemodialysis patients.In the study of serum sodium, the results indicated that there was a significant decrease in serum sodium level in the whey beverage groups, which showed a difference between the whey beverage group and the control group, while no effects have been found regarding vitamin E consumption and serum sodium levels in hemodialysis patients in the vitamin E group. It is noteworthy to mention that the decrease in the serum sodium in the group consuming whey beverage relates to the low sodium content of the beverage.

Meanwhile, in the case of serum potassium, a significant decrease in the levels of this electrolyte was observed in the vitamin E group during the 2 month period. There was also a significant difference between the vitamin E group and the control group, as well as the group of whey beverage with the control group. In the study of the effect of vitamin E on serum electrolytes in hypercholesterolemic rabbits within 4 months, the results of this study on serum sodium were consistent with our study and demonstrated no significant change. However, there was no significant modification in potassium (16), which is different from the present study, and can be due to the differences in the types of the patients studied or the duration of the study.

The low potassium content of whey beverage and their replacement instead of potassium-containing protein sources is a justification for the observed effect on serum potassium reduction in patients drinking whey beverage compared to the control group.On the other hand, oxidative stress leads to an increase in the activity of the K-ATP pump (17), so, consuming vitamin E as an antioxidant, while reducing the oxidative stress, decreasing the activity of the K-ATP pump. This prevents the outflow of potassium to the outside of the cell and affects the reduction of serum levels of potassium. Therefore, the observed effect on the reduction of serum potassium in the vitamin E group, is justifiable.

One of the limitations of the study is the short duration of the study, and lack of blinding.In addition, in the present study, no intervention (such as placebo) was done in patients of the control group, which is the other limitation of the study. Among the strengths of this study, the researchers pointed out the proper cooperation of the patients with the researchers during the study, as well as the correct follow-up and patient adherence to the therapeutic methods.On the other hand, in order to ensure the safety of the consumable beverages, the status of the uremic patients was investigated during the study, so that consuming beverages were associated with any risk in hemodialysis patients.

In addition, the stages of beverage processing were carried out in one of the prestigious factories, with all the health and safety principles, and under the supervision of the engineers in the R&D (research and development) department of the factory, as well as the consultant of the food industry. All the microbial tests have been carried out to ensure the safety and health of the produced product. Therefore, it can be stated that processed, fermented whey beverage has a significant role in controlling the serum levels of electrolytes in hemodialysis patients, along with low sodium, potassium and phosphorus contents, and had no significant effect on the serum levels of these electrolytes.

On the other hand, the intake of vitamin E, as an antioxidant (18), also according to the stated mechanism, is effective in reducing serum potassium level. With further studies in this field, the role of whey protein in controlling serum phosphorus levels can be more precisely defined. In particular, the control of serum phosphorus levels is important in hemodialysis patients for decreasing mortality, and hospitalization. Many studies have emphasized the strategies for controlling serum phosphorus in this

group of patients.

Conclusion

Since most protein sources have high phosphorus, hemodialysis patients inevitably limit their protein intake in order to prevent the increase of serum phosphorus levels and its consequences. As a result, providing a low-phosphorous protein source that meets the protein needs of hemodialysis patients without adverse effects on the increase of serum phosphorus level is of particular importance. According to the results of the present study, whey beverage is important for this feature, and further studies on this protein and in these patients are needed.

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Conflict of Interest

None declared.

References

1 Samadani M, Sohrabi Z, Akbarzade M. Body Mass Index Paradox in Hemodialysis Patients. *Int J Nutr Sci*. 2017;2:185-188.

2 Sohrabi Z, Eftekhari MH, Eskandari MH, et al. Intradialytic Oral Protein Supplementation and Nutritional and Inflammation Outcomes in Hemodialysis: A Randomized Controlled Trial. *Am J Kidney Dis*.2016;68:122-30. DOI:10.1053/j.ajkd.2016.02.050. PMID:27086768.

3 Salehi M, Sohrabi Z, Ekramzadeh M, et al. Selenium supplementation improves the nutritional status of hemodialysis patients: a randomized, double-blind, placebo-controlled trial. *Nephrol Dial Transplant*. 2013;28:716-23. DOI:10.1093/ndt/gfs170. PMID:22764197.

4 Ekramzadeh M, Sohrabi Z, Salehi M, et al. Adiponectin as a novel indicator of malnutrition and inflammation in hemodialysis patients. *Iran J Kidney Dis*. 2013;7:304-8. PMID:23880808.

5 Owaki A, Inaguma D, Aoyama I, et al. Serum phosphate level at initiation of dialysis is associated with all-cause mortality: a multicenter prospective cohort study. *Ren Fail*. 2018;40:475-82. DOI:10.1080/0886022X.2018.1499530. PMID: 30153079.

6 Razzaque MS. The dualistic role of vitamin D in vascular calcifications. *Kidney Int*. 2011;79:708-14. DOI:10.1038/ki.2010.432.PMID: 20962746.

7 Blacher J, Guerin AP, Pannier B, et al. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension*. 2001;38:938-42. DOI:10.1161/hy1001.096358. PMID:11641313.

8 Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. *J Am Soc Nephrol*. 2008;19:213-6. PMID:18094365. DOI: 10.1681/ASN.2007080854.

9 National Kidney F. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42:S1-201. PMID: 14520607.

10 Fukagawa M, Yokoyama K, Koiwa F, et al. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. *Ther Apher Dial*. 2013;17:247-88. DOI:10.1111/1744-9987.12058. PMID: 23735142.

11 Masakane I, Nakai S, Ogata S, et al. An Overview of Regular Dialysis Treatment in Japan (As of 31 December 2013). *Ther Apher Dial*. 2015;19:540-74. DOI:10.1111/1744-9987.12378. PMID: 26768810.

12 Nakamura T, Fujisaki T, Miyazono M, et al. Risks and Benefits of Sodium Polystyrene Sulfonate for Hyperkalemia in Patients on Maintenance Hemodialysis. *Drugs RD*. 2018;18:231-5. PMID: 30097847. DOI:10.1007/s40268-018-0244-x.

13 Dunlop JL, Vandal AC, Marshall MR. Low dialysate sodium levels for chronic haemodialysis. *Cochrane Database Syst Rev*. DOI:10.1002/14651858.CD011204.pub2.2019;1:CD011204. PMID: 30646428.

14 Roozbeh J, Shahriyari B, Akmali M, et al. Comparative effects of silymarin and vitamin E supplementation on oxidative stress markers, and hemoglobin levels among patients on hemodialysis. *Ren Fail*. 2011;33:118-23. DOI:10.3109/0886022X.2010.541579. PMID: 21332331.

15 Ramakrishnan K, Braunhofer P, Newsome B, et al. The economic impact of improving phosphate binder therapy adherence and attainment of guideline phosphorus goals in hemodialysis patients: a Medicare cost-offset model. *Adv Ther*. 2014;31:1272-86. DOI:10.1007/s12325-014-0170-4. PMID: 25479935.

16 Prasad K. Effects of vitamin E on serum enzymes and electrolytes in hypercholesterolemia. *Mol Cell Biochem*. 2010;335:67-74. DOI:10.1007/s11010-009-0243-x. PMID: 19730989.

17 Liu Y, Gutterman DD. Oxidative stress and potassium channel function. *Clin Exp Pharmacol Physiol*. 2002;29:305-11. PMID: 11985541. DOI:10.1046/j.1440-1681.2002.03649.x.

18 Sohrabi Z, Eftekhari MH, Akbarzadeh M,et al. Effect of Whey beverage fortified with vitamin E on quality of life in hemosialysis patients. *Int J Nutr Sci*. 2017;2:85-91.