ORIGINAL RESEARCH

The Effect of Egg White Meal on Anemia in Patients on Hemodialysis Taking Erythropoietin and Iron Infusion

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Objective: Eggs are a useful and cheap food source. We evaluated the effects of egg white meal on anemia in dialysis patients.

Methods: In an open-label, clinical trial, conducted in dialysis centers, 107 hemodialysis patients aged ≥ 18 years with hemoglobin levels below 12 g/dL and requiring treatment with artificial erythropoietin and iron infusion were included in the study. They were divided into a control and an intervention group. The participants in the intervention group consumed an egg white pack (containing 6 egg whites, 96 calories, 24 g protein) as a substitute for meat products 3 days a week for 8 weeks. Finally, changes in serum albumin, hemoglobin, ferritin and iron/total iron-binding capacity, erythropoietin dose, and iron infusion dose were measured.

Results: A total of 107 dialysis patients were studied (55 patients in egg white and 52 in control groups) with the mean age of 54.31 ± 16.35 years and male majority (57.90%). The mean of hemoglobin concentration had no statistically significant difference at baseline (P = .13) and after 4 weeks (P = .48), while after 8 weeks, the mean hemoglobin concentration in the intervention group was significantly higher than the control group (P = .03). Mean of synthetic erythropoietin dose after 4 and 8 weeks was significantly lower in the intervention group compared to the control group (P = .30, P = .001). Lower Erythropoietin Resistance Index values in intervention group were significantly higher than the control group (P = .02).

Conclusion: We observed that consumption of egg whites led to an increase in mean hemoglobin concentration, serum iron, and albumin levels. These results suggest that egg whites could be a useful dietary intervention for dialysis patients with anemia.

Keywords: anemia; dialysis; egg white; end-stage renal disease; protein diet

Introduction

END-STAGE RENAL DISEASE (ESRD) is a rapidly growing disease worldwide, including in the Middle East, where it is projected to increase to 18% by 2030.[1,2] The prevalence of chronic kidney disease in Iran is estimated at an average of 15.14%.[3] Despite advancements in treatment and dialysis techniques, the mortality rate for ESRD patients is 10-30 times higher than that of the general population.[4,5]

Proper nutrition is receiving more attention as an important factor in increasing the life expectancy of hemodialysis patients. Anemia and hypoalbuminemia are among the main criteria used to determine life expectancy in dialysis patients.[6] The primary pathophysiology in anemia in people with ESRD is erythropoietin deficiency and increased resistance to it. However, the lack of erythropoietin in dialysis patients is not the only cause of anemia. In fact, approximately 30% of dialysis patients still suffer from anemia despite receiving enough iron and erythropoietin, according to a study.[7]

Loss of appetite and subsequent lack of proper nutrition in hemodialysis patients can reduce sensitivity to erythropoietin and lower life expectancy in these patients.[8]

Unfortunately, decreased appetite and insufficient nutrition in hemodialysis patients have a significant prevalence.[9,10] Eggs have always been a main food source due to their low price, high nutritional value, abundance, and easy digestion.[11] They contain vitamin B12 and iron, which

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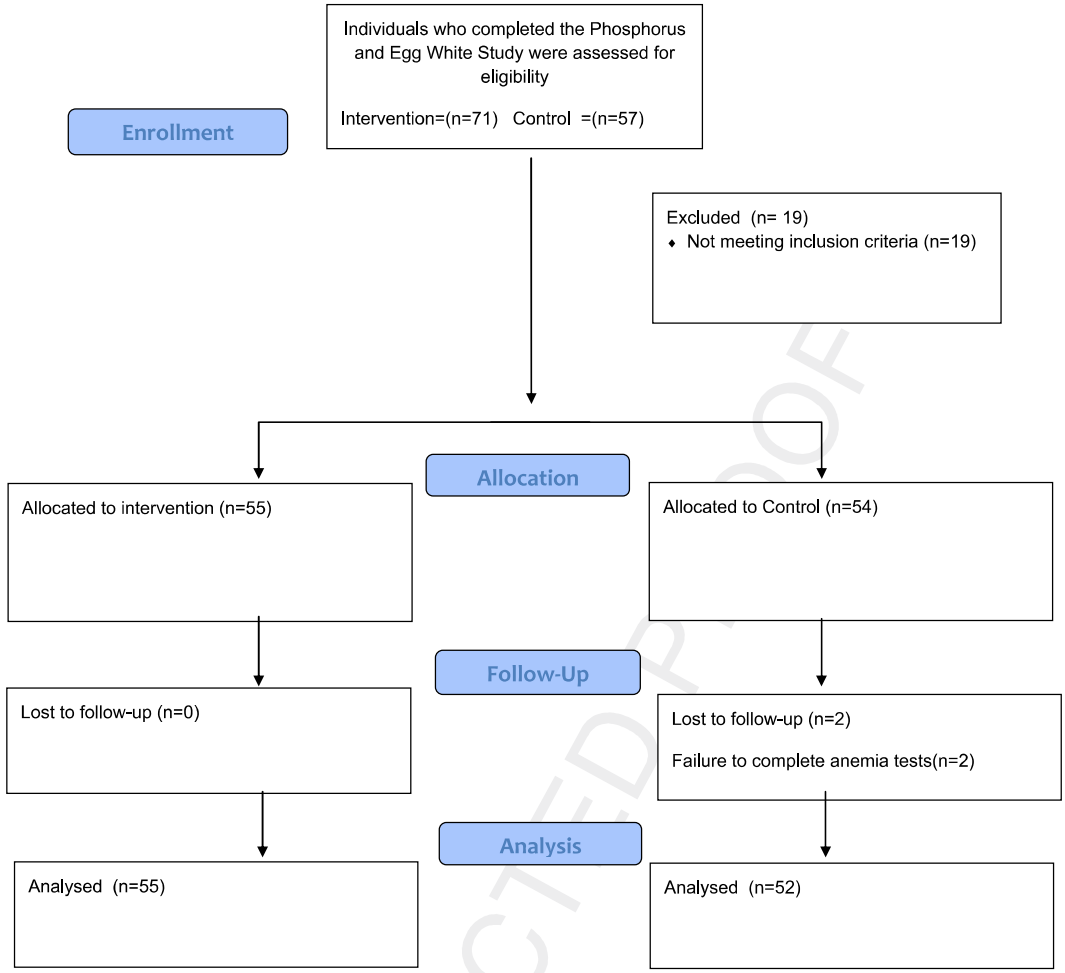

Figure 1. Flow chart of the study.

help with megaloblastic anemia and iron deficiency.[12] In addition, it has been shown that an egg white diet can accelerate the recovery process of iron deficiency anemia.[13]

While egg white is considered a rich source of albumin,[14] some studies contradict previous findings that it has a significant effect on the life expectancy of hemodialysis patients.[6] However, they do not have a negative impact on hope for survival. Nonetheless, eggs remain a rich, readily available, and less harmful source worthy of further study and investigation to potentially create positive effects on anemia in hemodialysis patients.

Materials and Methods

This open-label, parallel-group, per protocol clinical trial study was conducted in dialysis centers from September 2020 to January 2021. We were investigating the effect of egg white diet on phosphorus in dialysis patients when we noticed late in the study that some patients had both anemia and hyperphosphatemia. Therefore, we retrospectively reviewed trials before and after egg white meal administration in relation to anemia.

The statistical population for this study comprised hemodialysis patients who were talking erythropoietin and iron infusion. A sample size of 53 subjects per group was calculated using G-power software and considering an effect size of 0.55.

Initially, 150 patients were included in the study plan. In this study plan, anemia in hemodialysis patients was defined as having hemoglobin levels below 12 g/dL and requiring treatment with artificial erythropoietin. Patients who had uncontrolled egg allergies or pre-existing liver, cardiopulmonary, or psychiatric conditions were excluded from the study.

During the study, the patients were treated with subcutaneous Cinnapoietin (Erythropoietin β; 4,000 or 10,000 IU/0.6 mL; CinnaGen co., Tehran, Iran) and intravenous Hematofer (Iron Sucrose, 100 mg, Darou Pakhsh co., Tehran, Iran) according to monthly tests and under the supervision of a nephrologist.

To calculate the Erythropoietin Resistance Index (ERI), the weekly dose of artificial erythropoietin was calculated based on the patient's weight and then divided by their

Table 1. The Demographic Data of the Egg White and Control Groups

		Egg White	Control	*P*
Age		54.78 ± 17.15	53.82 ± 15.61	.764
Gender, *N (%)*	Male	36 (65.5)	26 (50.0)	.106
	Female	19 (34.5)	26 (50.0)	

Data presented as mean ± standard division.

hemoglobin level. A high ERI was defined as a value more than or equal to 11.52 units per week/g/dL/kg.[15] After recording the patients' information, the participants were divided into a control group and an intervention group using the random allocation rules technique. Participants were randomly assigned to groups through envelopes selection.

After selecting the anemia patients from the 2 groups, then height and weight and tests of albumin, hemoglobin, ferritin, and iron/total iron-binding capacity and dialysis adequacy before starting the diet. Egg white was recorded retrospectively based on patients' records. The case group was subjected to the egg white meal for 8 weeks as a meal 3 times a week at home and without any additives from the egg white package (Talavang co., Tehran, Iran.) contained cooked and rolled 6 egg whites with 96 kcal and 24 g of protein. At the end of the fourth and eighth weeks in this patient's blood levels of albumin, hemoglobin, ferritin, and iron/total iron-binding capacity were entered in the form. The administration of artificial erythropoietin and injectable iron used by the participants were recorded in the final data collection form. In the control group, there was no intervention, and only the phosphorus-limiting diet, which was given due to the phosphorus plan, was evaluated in both the control and intervention groups every week by a trained student and ward nurse.

Statistics

The collected data were reported descriptively by mean (± standard deviation) and frequency (percentage). Data analysis was performed by SPSS software, version 22 (SPSS Inc., Chicago, IL). Independent *t*-test or its nonparametric equivalent (Mann-Whitney test) was used to compare the means of the quantitative variables between the 2 groups. Paired *t*-test or its nonparametric equivalent, Wilcoxon test, was used for comparison of before and after values. Also, 2-way repeated measure was employed to compare hemoglobin concentration and synthetic

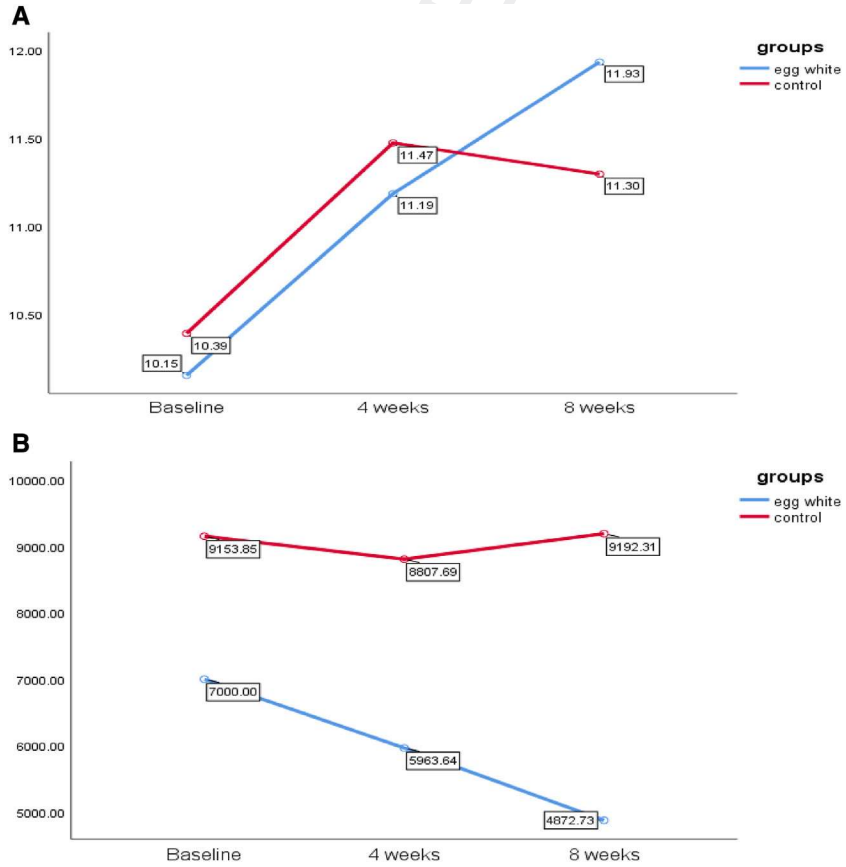

Figure 2. The comparison of hemoglobin concentration (A) and synthetic erythropoietin dose (B) at baseline and after 4 and 8 weeks.

Table 2. The Comparison of the Biochemical Variables at Baseline and After 8 Weeks

Parameter	Group	Baseline	After 8 weeks	*P*
Iron infusion dosage	Intervention	323.63 ± 46.78	143.63 ± 45.29	.001*
	Control	261.53 ± 48.10	467.30 ± 46.58	.001*
P		.350	.001*	
Ferritin	Intervention	275.87 ± 38.12	329.29 ± 48.41	.010*
	Control	306.76 ± 38.84	311.61 ± 49.33	.662
P		.57	.79	
Serum Iron	Intervention	55.00 ± 4.62	79.14 ± 5.58	.001*
	Control	65.76 ± 4.75	55.84 ± 5.74	.003*
P		.108	.004*	
TIBC	Intervention	276.01 ± 11.47	268.69 ± 10.39	.806
	Control	293.78 ± 11.79	278.13 ± 10.68	.169
P		.28	.52	
Albumin	Intervention	4.00 ± 0.06	4.45 ± 0.06	.001*
	Control	4.11 ± 0.06	4.10 ± 0.06	.984
P		.24	.001*	
KTV	Intervention	1.33 ± 0.04	1.28 ± 0.03	.267
	Control	1.43 ± 0.04	1.36 ± 0.04	.404
P		.17	.18	
URR	Intervention	0.681 ± 0.01	0.668 ± 0.01	.225
	Control	0.685 ± 0.01	0.680 ± 0.01	.651
P		.88	.67	
ERI	Intervention	10.86 ± 1.52	6.85 ± 1.37	.001*
	Control	13.26 ± 1.57	13.41 ± 1.90	.612
P		.27	.006*	

Data presented as mean ± standard division.
ERI, Erythropoiesis resistance index; TIBC, total iron-binding capacity; URR, urea reduction ratio. Q7

erythropoietin dose at baseline and after 4 and 8 weeks between the 2 groups. Significant level was considered as 0.05.

Results

A total of 107 dialysis patients were studied (Figure 1) (55 patients in egg white and 52 in control groups) with the mean age of 54.31 ± 16.35 years and male majority (57.90%). There was no statistically significant difference between the 2 groups based on demographic data (Table 1).

The mean of hemoglobin concentration had no statistically significant difference at baseline ($P = .13$) and after 4 weeks ($P = .48$), while after 8 weeks, the mean hemoglobin concentration in the intervention group was significantly higher than the control group ($P = .03$; Figure 2).

Also, the mean of synthetic erythropoietin dose had no statistically significant difference at baseline ($P = .06$), while after 4 and 8 weeks was significantly lower in the intervention group compared to the control group ($P = .30$, $P = .001$).

No statistically significant difference for other biochemical variables was demonstrated at baseline between the 2 groups (Table 2). After 8 weeks, we found a statistically significant difference on iron infusion dosage, serum iron, albumin, and ERI (Table 2).

No statistically significant difference for ERI frequency at baseline between 2 groups. The number of lower ERI in the intervention group was significantly higher than the control group after 8 weeks ($P = .02$) (Table 3).

Table 3. The Comparison of ERI Frequency Between 2 Groups

		Egg White	Control	*P*
Before	Low	35 (63.6)	24 (46.2)	.06
	High	20 (36.4)	28 (53.8)	
After	Low	44 (80.0)	31 (59.6)	.02
	High	11 (20.0)	21 (40.4)	
P		.001	.008	

ERI, Erythropoiesis resistance index.

Discussion

In this study, we aimed to investigate the impact of an egg white diet on anemia in dialysis patients over a period of 8 weeks. The results showed that after 8 weeks, the intervention group had significantly higher mean hemoglobin concentration, serum iron, and albumin levels compared to the control group. Additionally, the intervention group required a lower dosage of iron infusion and synthetic erythropoietin. Furthermore, the control group had significantly higher ERI values compared to the intervention group. It is worth noting that the patients who completed the study did not report any side effects during the intervention period. The administration of egg whites 3 times a week proved to be a feasible supplementary regimen due to its low cost, ease of administration, and good tolerability.

Anemia not only causes symptoms such as palpitations, fatigue, and shortness of breath, negatively impacting the quality of life for hemodialysis patients, but it also serves as an important prognostic indicator for poor outcomes in these patients.[16] A meta-analysis comprising 31 trials revealed a potential positive association between erythropoietin dose and all-cause mortality regardless of hemoglobin levels. Additionally, a high ERI was found to be a significant predictor of both all-cause mortality and cardiovascular mortality in patients undergoing maintenance hemodialysis.[16,17]

The pathogenesis of renal anemia involves various factors, including dysfunction of the erythropoietin axis, reduced lifespan of red blood cells, nutritional factors, occult and iatrogenic blood losses, and other contributors.[18] One potential cause of anemia in individuals with ESRD is a deficiency in iron. Kobayashi et al. conducted a study that showed the effectiveness of egg white protein in recovering from iron deficiency anemia. They identified ovalbumin as one of the beneficial components of egg white protein, while egg yolk protein was found to delay the recovery process. This study highlights the variability in the bioavailability of dietary iron depending on the protein source.[13] In another study by Werner ER et al., it was observed that the consumption of eggs daily for 6 months did not have any impact on iron status or the prevalence of anemia in young Malawian children.[19] This outcome could be attributed to the simultaneous intake of egg yolk protein along with egg white, which may have counteracted the beneficial effects of egg white in facilitating the absorption of iron.

Recently, it has been acknowledged that renal anemia exhibits important similarities with anemia of inflammation. One of the contributing factors to anemia in chronic kidney disease is the presence of interleukin-6, which contributes to the development of anemia through various mechanisms. These mechanisms include the induction of hypoferremia (low iron levels), exacerbation of renal fibrosis, and disruption of the erythropoietin axis.[18] In a study conducted by Kalantar-Zadeh et al., it was discovered that diminished appetite (anorexia) in patients with ESRD is associated with higher concentrations of proinflammatory cytokines. Additionally, these patients showed higher levels of erythropoietin hypo responsiveness and experienced poor clinical outcomes. This included a 4-fold increase in mortality, higher rates of hospitalization, and a lower quality of life among patients undergoing maintenance hemodialysis. The assessment of appetite status can provide valuable insights into the clinical condition of dialysis patients.[8,10] The data obtained from clinical trials examining the association between egg consumption and inflammation have yielded mixed results. Some studies have indicated that eggs can increase inflammation,[20] while others have suggested that they may actually decrease it.[21] However, a meta-analysis conducted on this topic demonstrated that egg consumption did not have a significant impact on serum biomarkers of inflammation in adults.[22]

In patients with ESRD, a variety of metabolic changes can occur, such as acidosis, systemic inflammation, and hormonal imbalances. These changes, combined with comorbidities and the use of multiple medications, can contribute to malnutrition and deficiencies in folic acid and vitamin B12.[23] As a result, incorporating eggs into the diet can be a beneficial strategy, as they are a rich source of complete protein and essential B vitamins, including B2, B12, and folate.[12]

Our study is the first to investigate the impact of egg white consumption on anemia in hemodialysis patients. However, there are several limitations to our study. First, the retrospective nature of the study and the limited follow-up period may have affected the accuracy and reliability of the results. Additionally, the lack of a crossover design may have limited our ability to draw definitive conclusions. To address these limitations, future studies should consider using a crossover design with a longer follow-up period. Furthermore, it is recommended that future studies examine a broader range of laboratory variables, such as normalized protein catabolic rate, and explore the impact of egg white consumption on inflammatory variables, such as C-reactive protein and interleukin-6.

Conclusion

Our study's findings indicate that egg whites' diet may have potential as a beneficial source of protein for dialysis patients. Specifically, we observed that consumption of egg white meal led to an increase in mean hemoglobin concentration, serum iron, and albumin levels. Additionally, we found that patients required a lower dosage of Venofer and synthetic erythropoietin when consuming egg white diet.

Practical Application

These results suggest that egg white meal could be a useful dietary intervention for dialysis patients with anemia due to its low cost, ease of administration, and good tolerability.

Ethical Consideration Statement

Data collection forms were anonymous and fiduciary, confidential, and nondisclosure of participants' secrets. Ethical consent was obtained from all patients. This research with the ethical code IR.KMU.AH.-REC.1400.330 was approved by the ethics committee of Kerman University of Medical Sciences.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

CRediT Authorship Contribution Statement

Jalal Azmandian: Methodology, Investigation, Formal analysis, Data curation, Writing –review & editing, Writing – original draft. **Najmeh Shamspour:** Methodology, Investigation, Formal analysis, Data curation, Writing –review & editing, Writing – original draft. **Ali Azmandian:** Methodology, Investigation, Formal analysis, Data curation, Writing –review & editing, Writing – original draft. **Habibeh Ahmadipour:** Investigation, Formal analysis, Data curation. **Tahereh Alinaghi Langari:** Investigation, Formal analysis, Data curation.

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