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Randomized Control Trials

The impact of oat (*Avena sativa*) consumption on biomarkers of renal function in patients with chronic kidney disease: A parallel randomized clinical trial

Mohammad Hossein Rouhani [a], Mojgan Mortazavi Najafabadi [b], Pamela J. Surkan [c], Ahmad Esmaillzadeh [d, g, h], Awat Feizi [e], Leila Azadbakht [a, d, f, *]

[a] Food Security Research Center and Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Kidney Diseases Research Center and Division of Nephrology, Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[c] Department of International Health, John Hopkins School of Public Health, Baltimore, USA
[d] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[e] Department of Epidemiology and Biostatistics, Isfahan University of Medical Sciences, Isfahan, Iran
[f] Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[g] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[h] Obesity and Eating Habits Research Center, Endocrinology and Metabolism Molecular -Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

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SUMMARY

Background & objective: Animal studies report that oat (*Avena sativa* L) intake has favorable effects on kidney function. However, the effects of oat consumption have not been assessed in humans. The aim of this study was to examine the impact of oat intake on biomarkers of renal function in patients with chronic kidney disease (CKD).

Methods: Fifty-two patients with CKD were randomly assigned to a control group (recommended to reduce intake of dietary protein, phosphorus, sodium and potassium) or an oat consumption group (given nutritional recommendations for controls +50 g/day oats). Blood urea nitrogen (BUN), serum creatinine (SCr), urine creatinine, serum albumin, serum potassium, parathyroid hormone (PTH), serum klotho and urine protein concentration were measured at baseline and after an eight-week intervention. Creatinine clearance was calculated using urine creatinine concentration.

Results: Within group analysis showed a significant increase in BUN ($P = 0.02$) and serum potassium ($P = 0.01$) and a marginally significant increment in SCr ($P = 0.08$) among controls. However, changes in the oat group were not significant. In a multivariate adjusted model, we observed a significant difference in change of serum potassium (−0.03 mEq/L for oat group and 0.13 mEq/L for control group; $P = 0.01$) and a marginally significant difference in change of serum albumin (0.01 g/dl for oat group and −0.08 for control group; $P = 0.08$) between the two groups. There was no change in PTH concentration.

Conclusion: Intake of oats may have a beneficial effect on serum albumin and serum potassium in patients with CKD.

Registration code: Present study registered under IRCT.ir identifier no. IRCT2015050414551N2.

1. Introduction

Chronic kidney disease (CKD) refers to a wide range of conditions affecting kidney structure and function [1]. Although CKD has not been considered a major cause of total global mortality in the past three decades, in 2010 it ranked among the top twenty causes of mortality (2). Eight to 16% of the world's population suffered

Abbreviations: ANCOVA, analysis of covariance; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PTH, parathyroid hormone; SCr, serum creatinine.

* Corresponding author. Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, PO Box 81745, Isfahan, Iran. Fax: +98 311 6682509.
E-mail address: azadbakht@hlth.mui.ac.ir (L. Azadbakht).

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from CKD in 2013 [2]. The prevalence of CKD among Iranian adults (18.9%) was higher than the estimated global average [3].

Whole dietary intake is related to chronic disease [4] and dietary intervention is a standard component of disease management for patients with CKD [5]. A diet low in protein, sodium, potassium and phosphorus is recommended for these patients [6]. Also, fruits, vegetables, whole grains and legumes are typically restricted in order to reduce phosphorus and potassium intake [6], and in turn reduce dietary fiber intake. Nevertheless, recent scientific evidence emphasizes important effects of fiber intake in adults with CKD [7]. Oats (*Avena sativa* L.) are a type of cereal grain and a source of dietary fiber. Specific components common in oats include beta-glucan (3–5%), a soluble fiber with cholesterol lowering effects [8]. Further, studies have reported cholesterol lowering effects of oats in clinical trials [9–11]. Lipid abnormalities are common among subjects with CKD [12] and lipid profiles may be used as predictors of CKD progression [13]. Also, oat beta-glucan appears to have a favorable effect on hyperglycemia and glucose homeostasis [14]. Moreover, anticancer properties have been reported for oat beta-glucan via upregulation of caspase-12 [15].

Polyphenolic compounds are plentiful in oats [16]. These components are cardioprotective [17] and have antioxidant properties [18]. Polyphenols have favorable effects on vascular tone, atherosclerosis, lipid oxidation and inflammation [19]. Avenanthramides are bioavailable hydroxycinnamoylanthranilate alkaloids found in oat bran, unique to oats [20]. Avenanthramides have shown antioxidant activity in humans [20].

As reported previously [21,22], inflammation contributes to onset and progression of CKD. Increased C-reactive protein concentration has been observed among subjects with CKD [23]. Moreover, oxidative stress is another factor contributing to CKD [24]. It appears that high prevalence of cardiovascular disease among patients with CKD may be due to increases in inflammatory markers and oxidative stress [25].

Although data are lacking regarding effects of oat consumption on human kidney function, animal research shows favorable effects of oat bran consumption on biomarkers of kidney disease and renal histology [26]. Also oat consumption has been shown to result in suppression of diabetic nephropathy via regulation of gene expression in rats [27].

We hypothesized that oats may have beneficial effects on patients with CKD due to its favorable effects on inflammation, oxidative stress and lipid profile. The aim of this study was to examine the effects of oat consumption on renal function in patients with CKD.

2. Subjects and methods

2.1. Subjects

This parallel randomized clinical trial was conducted in Isfahan, Iran from May 2014 to March 2015. Subjects were recruited from nephrology clinics and approached by physicians. Physicians performed biochemical tests for each subject and calculated the estimated glomerular filtration rate (eGFR). Patients were eligible if they were diagnosed with CKD, were not on a specific diet and had not started using a new CKD medication during the last two weeks. CKD diagnosis was defined as eGFR lower than 60 mL/min/1.73 m^2 [28]. We calculated eGFR for each patient using the Modification of Diet in Renal Disease (MDRD) equation [29]. Stages of CKD were defined in relation to eGFR values (stage 3: $30 \leq$ eGFR ≤ 59 mL/min/1.73 m^2; stage 4: $15 \leq$ eGFR ≤ 29 mL/min/1.73 m^2; stage 5: eGFR <15 mL/min/1.73 m^2) [28]. Low compliance with recommendations, use of new CKD medications and change in dose of prior medications were exclusion criteria.

Sixty patient volunteers with CKD were recruited for the present study. All eligible patients participated in an introductory meeting and received comprehensive information about the study. Volunteers signed informed written consent forms. Sample size was determined by $N = 2\,[(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times S^2]/d^2$ [30] where $\alpha = 0.05$ (type one error) and $\beta = 0.20$ (type two error). The required sample size was calculated based on the variance of blood urea nitrogen (BUN). Previous research shows that the variance of BUN in a population of Iranian patients with CKD was three [31]. The minimal detectable difference of BUN was 2.2 mg/dl. According to this formula, 25 patients were necessary for the study in each group. The Research Council and Ethical Committee of the School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran approved this study (Code: IR.MUI.REC.1394.3.192). This randomized clinical trial was registered at IRCT.ir (IRCT2015050414551N2).

2.2. Study procedure

Patients were randomly assigned to nutritional recommendations or nutritional recommendations +50 g of oat flour per day. Randomization was performed using SPSS 20 software (IBM). The intervention lasted 8 weeks. Given this was a food-based intervention, participants could not be blinded. Nevertheless, clinical laboratory personnel were blinded to intervention groups. Intervention groups were matched for sex and stage of CKD. Patients completed visits scheduled at baseline and 2-, 4-, 6- and 8-weeks. Subjects were requested to bring a one-day food diary at the 2nd, 4th and 6th week of the intervention. Thus, three one-day food records were collected from each patient (on two weekdays and one weekend day). A study dietitian evaluated the completeness of food records with each participant.

2.3. Dietary intervention

Participants in the control group received nutritional recommendations for patients with CKD to reduce intake of dietary protein, phosphorus, sodium and potassium. These nutritional recommendations were based on the dietary guidelines of U.S National Library of Medicine [6]. Patients were asked to reduce the consumption of dairy, cheese, different types of meat (especially red and processed meat), eggs, high potassium fruits and vegetables, salt and salty foods, legumes and whole grains. A list of prohibited high potassium fruits and vegetables and salty foods was provided to subjects (Supplement 1) [6]. Also, we provided lists of fruits and vegetables with low- to medium- potassium content and instructed patients that they were allowed to consume two servings per day [6]. Similar nutritional recommendations, including the list of prohibited fruits and vegetables and list of fruits and vegetables with low- to medium- potassium content were provided for patients in the oat consumption group. In both groups, the criteria for compliance with nutritional recommendations included protein intake lower than 0.8 g/kg, sodium intake lower than 3000 mg, phosphorus intake lower than 1000 mg and potassium intake lower than 2400 mg [32,33]. We analyzed food records to obtain dietary intakes of nutrients using the USDA database.

The nutrient composition of oat flour was analyzed according to the Association of Analytical Communities methods [34]. The protein, carbohydrate and fat content of oat flour were 15.62, 67.54 and 6.54 g/100 g, respectively. As shown in Table 1, the phosphor content of oat flour was 248.20 mg/kg. Since the upper limit of phosphorus intake for a patient with CKD is 1000 mg per day [32,33], we prescribed 50 g of oats to provide only 1% of allowed phosphorus intake level. Whole oat grain seeds were milled and packed in 150-

Table 1
The nutrient composition of oat flour.

Ingredients	Amounts
Protein (g/100 g)	15.62
Carbohydrate (g/100 g)	67.54
Fat (g/100 g)	6.52
Phosphorus (mg/kg)	248.20
Moisture (g/100 g)	6.60
Ash (g/100 g)	3.75

Oat flour was analyzed in the Meyar Danesh Pars laboratory according to the Association of Analytical Communities methods.

g packages. Each package contained three days' worth of oats. We used aluminum-based packaging to protect oat flour from the light and air. Patients in the oat group were instructed to consume 50 g of oat flour per day and were provided with an oat porridge recipe. They were further instructed to consume porridge without salt and sugar. Every two weeks, patients were supplied with a sufficient supply of oat packages. In visits every two weeks, oat consumption was monitored. Also, compliance with oat consumption was evaluated using an oat consumption checklist. Patients were asked to mark the appropriate checkbox after consuming oat porridge each day. Also, we monitored the number of consumed oat packages. Patients who were unable to consume $\geq$15% of the prescribed oat flour were excluded.

2.4. Biochemical measurements

After patients had fasted overnight for $\geq$10 h, a blood sample was collected in the early morning. Subjects were asked to collect a 24-h urine sample the previous day and to discard the first void of urination upon waking on day one. After that, they were instructed to collect all urine in a special container for the next 24 h, including the first void the following morning. Blood samples were coagulated and centrifuged at 3000 $\times$ g for 10 min to separate the serum. The enzymatic method based on urease was used to measure BUN (Pars Azmoon Inc, Tehran, Iran). Serum creatinine (SCr) and urine creatinine concentration was determined using spectrophotometric assays (Pars Azmoon Inc, Tehran, Iran). We used the Bromocresol Green method to measure serum albumin (Pars Azmoon Inc, Tehran, Iran). Serum potassium level was determined with a direct electrochemical technique. We measured parathyroid hormone (PTH) using an ELISA kit (Monobind Inc, Costa Mesa, CA). Also, serum klotho was measured using a similar method (Cusabio Human Klotho ELISA Kit, Wuhan, China). Urine protein concentration was determined using photometric methods (Pars Azmoon Inc, Tehran, Iran). Creatinine clearance was calculated using urine creatinine concentration [36].

2.5. Other variables

Weight was measured while patients wore light clothes and no shoes. We used self-reported height in this study.

2.6. Statistical analysis

The results of Kolmogorov–Smirnov test and histogram showed that the distributions of SCr, PTH, urine protein and BUN were not normal. Therefore, these variables were log transformed. Chi-square tests were performed to compare quantitative variables between groups. The difference in means of energy intake, protein intake per body weight, mean biomarkers at the beginning and end of the study and changes in biomarkers were checked between the oat and the nutritional recommendation groups using independent Student t-tests. Baseline values and endpoint measures were compared within each group using paired t-tests. Differences in energy-adjusted nutrient intakes were tested using analysis of covariance (ANCOVA). Mean difference in biomarkers of renal function were computed as final measures minus baseline values. We used both a crude and a multivariate adjusted model (adjusted for age, height, weight change and dietary protein intake) to compare mean differences between the oat consumption and nutritional recommendation groups. Independent student t-test and analysis of covariance were used in crude and in multivariate adjusted models, respectively. We used means and standard deviations to present continuous data. SPSS version 20 statistical software was used to carry out data analysis.

3. Results

Among the sixty recruited patients, eight individuals withdrew because of low compliance, change in phone number or other reasons (Fig. 1). Finally, data from fifty-two patients (twenty-six subjects in each group) were included in the analysis.

Baseline characteristics of patients in each group are shown in Table 2. Mean ages in the oat and the nutritional recommendation groups were 60.46 y and 56.50 y, respectively ($P = 0.24$). We found no statistically significant difference in weight ($P = 0.33$), height ($P = 0.17$) and body weight status ($P = 0.94$) between the two groups.

Table 3 demonstrates nutrient intake obtained from food diaries in patients with CKD. The comparison between nutrient intake prior to and during the study showed that the dietary intervention resulted in lower intake of phosphorus, potassium, sodium and protein per body weight in both groups. The result showed that protein intake per body weight was lower than 0.8 g/kg in both groups. Moreover, sodium, potassium and phosphorus intake in both groups was lower than 3000, 2400 and 1000 mg/day, respectively. We observed that patients in the oat group consumed larger amounts of dietary fiber ($P = 0.01$) and phosphorus ($P = 0.02$) in comparison with the nutritional recommendation group. The differences between the two groups for other nutrients were not significant.

Table 4 displays baseline and post intervention serum and urine biomarkers of renal function in patients with CKD. Within group analysis showed a significant increase in BUN ($P = 0.02$) and serum potassium ($P = 0.01$) in the nutritional recommendation group. Also, a marginally significant increase in SCr was observed in this group ($P = 0.08$). Compared with baseline values, PTH was marginally decreased in both groups following the eight-week intervention ($P = 0.09$ in the oat group and $P = 0.05$ in the nutritional recommendations group). Between group analysis showed that patients in the oat group had higher baseline serum potassium compared with those in the nutritional recommendations group ($P = 0.04$).

Table 5 shows changes of serum and urine biomarkers of renal function among patients with CKD following the eight-week intervention. There was a statistical significant difference in change of serum potassium between the two groups, which remained significant after adjusting for confounders ($P = 0.01$). In a multivariate adjusted model, serum albumin was marginally reduced in the nutritional recommendation group compared to the oat group ($P = 0.08$).

4. Discussion

As our results show, although endpoint BUN, SCr and serum potassium were increased within the standard nutritional recommendation group from baseline to the end of the trial, there were no changes in these variables for the oat consumption group.

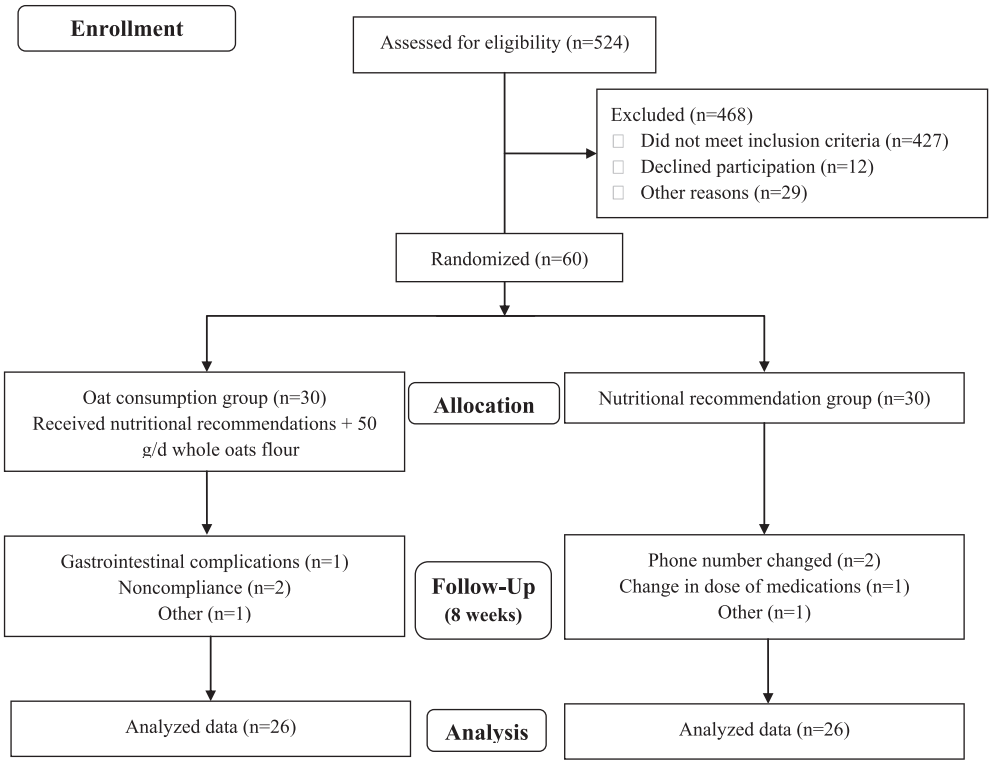

Fig. 1. Participant flow diagram.

Table 2
Baseline characteristics of patients with chronic kidney disease in the oat and the nutritional recommendation groups.

Variables	Oats group[a] (n = 26)	Nutritional recommendations group[b] (n = 26)	P value[c]
Age (year)	60.46±8.66[d]	56.50 ± 14.61	0.24
Male (%)	76.9	76.9	1.00
Weight (kg)	77.83 ± 13.73	74.50 ± 10.75	0.33
Height (cm)	168.65 ± 9.59	165.11 ± 9.83	0.17
BMI (kd/m^2)	27.29 ± 4.26	27.28 ± 2.97	0.99
Body weight status[e]			
Normal weight (%)	19.2	19.2	
Overweight (%)	57.7	61.5	
Obese (%)	23.1	19.2	0.94
CKD stage			
Stage 3 (%)	84.6	84.6	
Stage 4 (%)	15.4	15.4	1.00

CKD: chronic kidney disease.
[a] Subjects were instructed to consume 50 g oat flour per day + nutritional recommendations for patients with chronic kidney disease (including following a low protein diet and avoiding salt and foods rich in potassium and phosphorus).
[b] Nutritional recommendations for patients with chronic kidney disease included a low protein diet and avoidance of salt and foods rich in potassium and phosphorus.
[c] Calculated by independent t-tests and chi-square tests for quantitative and qualitative variables, respectively.
[d] All values are Mean ± SD except for male, body weight status and CKD stage presented as percentages.
[e] Body weight status was categorized using body mass index (BMI) categories (normal weight: 18.5 < BMI < 25 kg/m^2, overweight: 25 ≤ BMI < 30 kg/m^2 and obese BMI ≥ 30 kg/m^2).

Moreover, serum potassium showed a significant positive change in the nutritional recommendation group in comparison with the oat consumption group. This is the first randomized clinical trial that has investigated the results of oat consumption on kidney function in humans. Moreover, we used a novel biomarker of renal function (i.e., serum klotho) in this study.

We observed that the phosphorus content of oats consumed was 248.20 mg/kg. This contrasts with the USDA food composition analysis value of 5230 mg/kg for the phosphorus content of oats [37]. There was no remarkable difference in protein, carbohydrate and fat content between oats used in our study and the USDA report. However, we used organic oats grown without phosphate fertilizer. Therefore, phosphorus content of oats used was lower than in the USDA report. As phosphorus intake has been restricted in patients with CKD, organic whole grains grown without phosphate fertilizer give these patients an opportunity to consume higher amounts of dietary fiber.

The findings showed that the intake of phosphorus, potassium, sodium and protein per body weight was lower during the study in comparison with intake in either of the groups prior to the study. Although the dietary intervention resulted in beneficial changes in dietary intake of potassium and sodium, dietary intake of these nutrients prior to the study was within the recommended values range i.e., <2400 mg/day for potassium and <3000 mg/day for sodium. Also, pre-study protein intake per body weight was in the desired range (0.8 g/kg/day). Therefore, appropriate pre-study dietary intake may be a reason for no change in BUN and SCr.

The results showed that protein intake per body weight were lower than 0.8 g/kg in both groups. Moreover, sodium, potassium and phosphorus intake in both groups was lower than 3000, 2400 and 1000 mg/day, respectively. As mentioned in the methods, compliance with nutritional recommendations was evaluated using intake of protein (per body weight), sodium, phosphorus and potassium. This analysis showed that patients in both groups had overall good compliance with nutritional recommendations.

We observed that patients in the oat group consumed greater amounts of dietary fiber and phosphorus compared with those in the nutritional recommendation group. Because we used whole oat flour, rich in dietary fiber and phosphorus [37], it is likely that those differences are due to oats. Prior studies report that dietary fiber

Table 3
Reported nutrient intake obtained from food diaries among patients with chronic kidney disease in the oat and the nutritional recommendation groups.

Variables	Oat group[a] (n = 26)		P[c]	Nutritional recommendation group[b] (n = 26)		P[c]	P[f]
	Before	After		Before	After		
Energy (Kcal)	1533.61 ± 96.95	1384.33±313.17[d,e]	0.01	1593.27 ± 39.48	1352.56 ± 405.59	0.01	0.82
Protein (g)	51.63 ± 9.68	46.44 ± 8.26	0.71	54.32 ± 12.21	44.80 ± 8.26	0.05	0.37
Protein per body weight (g/kg)	0.81 ± 0.13	0.62 ± 0.16	0.01	0.83 ± 0.17	0.60 ± 0.17	0.01	0.44
Fat (g)	41.06 ± 8.55	47.33 ± 8.77	0.01	41.20 ± 14.38	47.68 ± 8.77	0.06	0.88
Saturated fatty acid (g)	12.29 ± 3.85	11.21 ± 3.67	0.91	11.14 ± 4.10	11.46 ± 3.65	0.22	0.65
Cholesterol (mg)	105.90 ± 43.36	81.37 ± 42.00	0.04	93.15 ± 44.37	83.05 ± 42.02	0.80	0.77
Carbohydrate (g)	239.51 ± 24.00	194.10 ± 20.23	0.01	251.07 ± 44.63	195.01 ± 20.25	0.01	0.78
Dietary fiber (g)	9.58 ± 3.57	13.41 ± 3.75	0.01	11.71 ± 4.20	10.73 ± 3.72	0.30	0.01
Sodium (mg)	1434.50 ± 339.93	1193.90 ± 513.57	0.04	1404.90 ± 429.84	1245.51 ± 513.67	0.04	0.68
Potassium (mg)	1892.87 ± 322.08	1642.58 ± 404.46	0.03	1982.22 ± 387.12	1718.70 ± 404.41	0.02	0.76
Phosphorus (mg)	1116.47 ± 128.01	921.90 ± 175.54	0.01	1239.95 ± 257.67	802.72 ± 175.55	0.02	0.04

[a] Subjects were instructed to consume 50 g oat flour per day + nutritional recommendations for patients with chronic kidney disease (including following a low protein diet and avoiding salt and foods rich in potassium and phosphorus).
[b] Nutritional recommendations for patients with chronic kidney disease included a low protein diet and avoidance of salt and foods rich in potassium and phosphorus.
[c] Comparisons between before and after measurements within each group.
[d] Mean ± SD.
[e] Values have been adjusted for total calorie intake except for energy and protein per body weight.
[f] Comparison of change in dietary intake between the two groups.

Table 4
Serum and urine biomarkers of renal function among patients with chronic kidney disease in the oat and the nutritional recommendations groups at baseline and following an 8-week intervention.

Variables[d]	Oat group[a] (n = 26)	Nutritional recommendation group[b] (n = 26)	P value[c]
BUN (mg/dl)			
Before	21.24±5.49[e]	19.48 ± 5.42	0.36
After	22.40 ± 5.47	22.16 ± 5.38	0.91
P	0.12	0.02	
SCr (mg/dl)			
Before	1.90 ± 0.29	1.84 ± 0.25	0.67
After	1.93 ± 0.30	1.92 ± 0.27	0.93
P	0.37	0.08	
Serum albumin (g/dl)			
Before	4.24 ± 0.32	4.20 ± 0.35	0.72
After	4.22 ± 0.31	4.15 ± 0.32	0.40
P	0.64	0.22	
Serum potassium (mEq/L)			
Before	4.54 ± 0.41	4.30 ± 0.36	0.04
After	4.49 ± 0.42	4.45 ± 0.38	0.74
P	0.20	0.01	
Parathyroid hormone (Pg/ml)			
Before	49.96 ± 5.84	52.35 ± 5.60	0.78
After	46.41 ± 5.82	49.47 ± 5.65	0.70
P	0.09	0.05	
Serum klotho (ng/dl)			
Before	2.85 ± 0.78	2.77 ± 0.62	0.67
After	2.81 ± 0.91	2.75 ± 0.70	0.81
P	0.41	0.73	
Urine protein (mg/24 h)			
Before	310.29 ± 6.47	465.77 ± 6.22	0.20
After	373.01 ± 6.44	436.29 ± 6.46	0.64
P	0.12	0.33	
Creatinine clearance (mL/min per 1.73 m^2)			
Before	45.60 ± 15.61	43.36 ± 15.70	0.61
After	44.60 ± 16.39	44.34 ± 13.29	0.95
P	0.50	0.78	

BUN: blood urea nitrogen, SCr: serum creatinine.
[a] Subjects were instructed to consume 50 g of oat flour per day + the nutritional recommendations for patients with chronic kidney disease (including following a low protein diet and avoiding salt and foods rich in potassium and phosphorus).
[b] Nutritional recommendations for patients with chronic kidney disease included a low protein diet and avoidance of salt and foods rich in potassium and phosphorus.
[c] P values have been calculated by independent t-tests and present comparisons of baseline and final values between the two groups.
[d] P values were calculated using paired t tests and present comparisons of baseline and final values within each group.
[e] Mean ± SD.

can have beneficial effects on kidney function in patients with CKD [5,7]. Therefore, consumption of whole oat flour may increase dietary fiber intake in these patients. Although oat consumption resulted in higher phosphorus intake, the amount of phosphorus was lower than the recommended levels (i.e., 1000 mg/day). Moreover, recent studies suggest that the source of dietary phosphorus may be more important than the amount of phosphorus intake in patients with CKD [38,39]. Inorganic dietary phosphorus found in processed foods and food additives has a high absorption rate [38]. Organic dietary phosphorus occurs in protein-rich (e.g., dairy, meats and eggs) and plant-based foods (e.g., whole grains and legumes) [39,40]. The bioavailability of organic phosphorus from plant-based foods is not usually high (20–50%) because it is in the form of phytate, and phytase (phytate-hydrolyzing enzyme), which is not expressed in humans [38]. Therefore, consumption of whole grains and legumes should not be severely restricted in patients with CKD [41]. It is important that nutritional recommendations for patients with CKD focus on the source of dietary phosphorus rather than absolute intake.

Although postprandial serum phosphorus level is directly associated with dietary intake of phosphorus [42], it does not reflect long-term phosphorus intake. An increase in the release of PTH was observed in subjects who consumed high phosphorus diets [43]. Therefore, we measured PTH concentration to ensure that increased dietary intake of phosphorus in the oat group had no adverse effects on phosphate homeostasis. As reported in our results, PTH marginally decreased in both groups following the eight-week intervention. Thus, it appears that higher phosphorus intake in the oat group did not result in higher serum phosphorus level of PTH because of low bioavailability of phosphorus in oats.

Within group analyses showed significant increases in BUN and serum potassium and a marginally significant increment in SCr in the nutritional recommendations group. However, the changes in the oat consumption group were not significant. Also, results indicate a significant difference in change of serum potassium between the oat group and nutritional recommendations group. These findings suggest that oat consumption may slow down progression of CKD. Previous studies reported that renal antioxidant status, antioxidant enzyme levels and histology of the kidney were improved in rats following consumption of a meal containing oats [26,44]. Moreover, another experimental study showed that oat intake had a favorable effect on SCr, glomerulus segmented

Table 5
Changes of serum and urine biomarkers of renal function among patients with chronic kidney disease in the oat and the nutritional recommendation groups following an 8-week intervention.

Variables	Oat group[a] (n = 26)	Nutritional recommendation group[b] (n = 26)	P value[c]
BUN (mg/dl)			
Crude	1.49±4.17[d]	2.59 ± 5.47	0.42
Model 1	1.91 ± 4.30	2.18 ± 4.28	0.84
SCr (mg/dl)			
Crude	0.03 ± 0.18	0.09 ± 0.26	0.37
Model 1	0.04 ± 0.23	0.09 ± 0.21	0.42
Serum albumin (g/dl)			
Crude	−0.01 ± 0.17	−0.05 ± 0.22	0.47
Model 1	0.01 ± 0.16	−0.08 ± 0.17	0.08
Serum potassium (mEq/L)			
Crude	−0.05 ± 0.19	0.14 ± 0.23	0.01
Model 1	−0.03 ± 0.22	0.13 ± 0.20	0.01
Parathyroid hormone (Pg/ml)			
Crude	−5.08 ± 11.35	−1.71 ± 8.63	0.23
Model 1	−4.65 ± 10.44	−2.14 ± 10.47	0.40
Serum klotho (ng/dl)			
Crude	−0.05 ± 0.28	−0.02 ± 0.23	0.67
Model 1	−0.05 ± 0.24	−0.01 ± 0.26	0.66
Urine protein (mg/24 h)			
Crude	103.73 ± 417.81	82.19 ± 277.59	0.83
Model 1	94.73 ± 355.34	91.19 ± 353.11	0.97
Creatinine clearance (mL/min per 1.73 m^2)			
Crude	−1.00 ± 7.40	0.98 ± 17.92	0.60
Model 1	0.03 ± 12.41	−0.05 ± 12.20	0.98

Model 1: Adjusted for age, height, weight change, dietary protein intake, energy intake and baseline values.
[a] Subjects were instructed to consume 50 g oat flour per day + the nutritional recommendations for patients with chronic kidney disease (including following a low protein diet and avoiding salt and foods rich in potassium and phosphorus).
[b] Nutritional recommendations for patients with chronic kidney disease included a low protein diet and avoidance of salt and foods rich in potassium and phosphorus.
[c] Calculated by independent t tests in crude model and analysis of covariance in adjusted model.
[d] Mean change ± SD.

sclerosis, tubule vacuolar degeneration and inflammatory markers [27]. Therefore, the beneficial effects of oat intake on kidney function could be mediated by polyphenolic compounds found in oats such as avenanthramides, ferulic acid, p-coumaric acid, syringic acid and vanillic acid [14]. Ferulic acid may slow down progression of diabetes nephropathy and has a favorable effect on oxidative stress and inflammation in the kidney [45–47]. P-coumaric acid is a protective agent against nephrotoxicity [48,49]. Also, syringicacid has high antioxidant properties [50]. Vanilic acid may increase nitric oxide production, improve renal function and serve as a protective agent against nephrotoxicity [51,52]. Moreover, avenanthramides are strong antioxidant agents found in oats [53]. As inflammation and oxidative stress have key roles in progression of CKD [21,22], the aforementioned polyphenolic compounds may improve kidney function in patients with CKD.

Serum albumin was marginally reduced in the nutritional recommendation group compared to the oat group after adjusting for confounders. There was an inverse association between inflammation and serum albumin level in patients with CKD [54]. Inflammation may lead to lower albumin synthesis and higher albumin fractional catabolic rate [55]. Patients in the oat group consumed higher amounts of anti-inflammatory compounds present in oats. Therefore, in essence, patients in the oat group consumed an anti-inflammatory diet.

In the present study, we measured serum klotho as a novel biomarker for kidney function. Klotho is a product of an aging-suppressor gene [56]. Klotho gene expression is down regulated by inflammatory markers [57]. Klotho contributes in calcium and phosphate reabsorption and potassium excretion in the distal tubule [58–60]. Serum klotho has an indirect association with serum creatinine and decreases in patients with CKD [56]. A previous observational study reported that serum klotho level decreased in patients with CKD and its concentration was associated with progression of CKD [61]. It seems that klotho may link CKD to cardiovascular morbidity and mortality [62]. However, future studies should examine this hypothesis. Regulation of klotho gene expression is complex [63]. It seems that hyperphosphatemia, hypercalcemia, ischemia, oxidative stress, angiotensin II, TGF-β1, and inflammation are factors that affect klotho expression in the kidney [64]. Long-term intervention by infusion of Ang II has been found to result in changes in klotho expression [64]. Therefore, long-term interventions should be conducted to assess the effect of dietary intakes on klotho level.

A limitation of this research was the short study duration. Similar long-term interventions should be conducted to confirm our findings. Additionally, the study's sample size was small. The results of our study should be confirmed by future studies with large numbers of patients with CKD. As there is no specific biomarker associated with intake of oats, we evaluated compliance with oat consumption using a self-reported method (checklist).

A strength of the current study is use of a 24-h urine sample to determine the glomerular filtration rate rather than eGFR. Also, we measured serum klotho as a novel biomarker of renal function. In the present study, phosphorus intake was assessed using PTH level rather than serum phosphorus. As serum phosphorus is strongly controlled by hormones, it is not a good indicator of phosphorus intake [65]. The matching of the intervention groups on stage of CKD and sex ratio was another strength of this study. Moreover, oats are not usually consumed by Iranians (e.g. they do not normally consume oatmeal or other oat containing dishes). Therefore, our findings are unlikely to be influenced by previous intake of oats.

In conclusion, oat intake may have beneficial effects on serum albumin and serum potassium in patients with CKD.

Conflict of interest

Authors have no conflict of interest.

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L.A, A.E, A.F and M.H.R designed the study. M.M.N, L.A and M.H.R collected the data. L.A and M.H.R ran statistical analyses and drafted the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2016.11.022.

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