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Original article

# Low protein diet score: a novel diet quality index and predictor of disease progression in patients with chronic kidney disease

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**Summary.** *Background and Aim:* Patients with chronic kidney disease (CKD) have been recommended to consume a low protein diet. However, there is no specific index for evaluating amounts of dietary protein and CKD progression in these patients. The objective of this study was to define a low protein diet score (LPDS) as a predictor of CKD progression and an index of diet quality in patients with CKD. *Methods:* For this cross-sectional study, two hundred twenty seven eligible subjects with CKD (stage 3 and 4) were selected. We used a validated food frequency questionnaire to assess dietary intake of patients. LPDS was defined based on the 3 cut of points: >2 gr/kg (score=1), 1.01-2 gr/kg (score=2) and ≤ 1 gr/kg (score=3). Renal function (i.e., blood urea nitrogen and serum creatinine) and cardiometabolic variables (i.e., low density lipoprotein, triglyceride, total cholesterol, fasting blood sugar and high sensitivity C-reactive protein) were measured by biochemical assessment. As dietary intakes of sodium, potassium, phosphorus, saturated fatty acid and cholesterol are important, we used intake of these nutrients to assess diet quality. *Results:* Patients who received higher scores, had better diet quality because they consumed lower amounts of phosphorus, potassium, saturated fatty acid and cholesterol (P<0.01 for all). Biochemical assessments showed that in comparison with the bottom LPDS, a marginally significant lower blood urea nitrogen was observed among subjects with higher scores (P=0.06). We did not observe any significant difference in other biochemical variables across the defined LPDS. After adjusting for all confounders, a significant decreasing trend for risk of CKD progression was revealed across LPDS (P for trend=0.04). *Conclusion:* The results of the present study showed that higher LPDS was associated with favorable nutrients intake (lower intakes of sodium, potassium, phosphorus, cholesterol and saturated fatty acid) among patients with CKD. Moreover, subjects who received higher LPDS had a marginally significant lower BUN. Also, we observed that LPDS was inversely related to the risk of being in the higher stage of CKD after adjusting for potential confounders. Therefore, it was a predictor of CKD progression.

**Key words:** chronic kidney disease, dietary protein, disease progression

## Abbreviations

BUN: blood urea nitrogen, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, FBS: fasting blood sugar, FFQ: food frequency questionnaire, hs-CRP: high sensitive C-reactive protein, LDL-C: low density lipoprotein cholesterol, LPDS: low protein diet score, SCr: serum creatinine, TC: total cholesterol, TG: triglyceride

## Introduction

Chronic kidney disease (CKD) is a health concern in developed and developing countries. Reported results from NHANES data revealed that 13.1% of American population suffers from CKD (1). CKD is more prevalent among Iranian adults (18.9%) (2).

Dietary recommendations have an important role in medical management of CKD. Evidence showed that higher dietary protein intake in healthy subjects may increase the risk of renal hypertrophy, glomerular hyperfiltration and renal blood flow (3). Therefore, patients with CKD are recommended to lower protein intake (4). Observational studies revealed that CKD progression was associated with the amount of consumed dietary protein (5). Also, an inverse association between low protein diet intake and risk of death from renal disease was observed in subjects with CKD (6).

Patients with CKD were recommended to restrict dietary sodium, potassium and phosphorus because excess amounts of these minerals cannot be excreted (4). Therefore, dietitians prescribe a diet restricted in sources of mentioned minerals such as fruits, vegetables, legumes, dairies and whole grains (7). These restrictions are in contrast with recommended diets for healthy subjects. For instant, according to the HEI-2010, consumption of fruits, vegetables, whole grains and low fat dairies should be increased (8). Therefore, general dietary recommendations for healthy subjects cannot be used to assess diet quality of the subjects with CKD. Assessment of diet quality is important in individuals with CKD because most patients suffer from malnutrition (9). Unfortunately, a specific index has not yet been defined to assess diet quality of patients with CKD.

In 2008, carbohydrate scoring was suggested by Halton et al. (10). They score dietary carbohydrate by using percentage of energy as carbohydrate to assess the association between a low carbohydrate diet and risk of diabetes because dietary carbohydrate was critical for type 2 diabetic patients (10). In the management of CKD, dietary protein is the most important macronutrient. The findings of researches emphasized that protein intake should be controlled in dietary management of CKD (11). Evidence revealed that high dietary protein intake was directly related to CKD progression (12). Therefore, we hypothesized that a low protein diet score (LPDS) may predict the progression of CKD. Scoring the dietary factors is a common practice in nutritional research and studies reported that interpretation regarding the relation between diet and disease may be easier by macronutrient scoring (10, 13, 14). However, dietary protein was not scored previously. Moreover, there is no specific diet quality index for evaluating the quality of diet in subjects with CKD. Therefore, the aim of current study was to define a LPDS as a predictor of CKD progression and an index of diet quality in patients with CKD.

## Methods

*Subjects:* This research was a cross-sectional study. Among patients who referred to clinics of nephrology, two hundred twenty one subjects with CKD were selected. Patients were chosen from both genders. We had no age restriction. A nephrologist calculated estimated glomerular filtration rate (eGFR) for each subject (15) and eGFR<60 mL/min/1.73m$^2$ was considered as CKD (16). CKD was categorized as stage 3 (30≤ eGFR ≤59 mL/min/1.73m$^2$), stage 4 (15≤ eGFR ≤29 mL/min/1.73m$^2$) and stage 5 (eGFR <15 mL/min/1.73m$^2$) (16). Written consent was signed by all patients.

*Dietary assessment:* Dietary intake of patients during the previous year was assessed by a validated (20, 21) food frequency questionnaire (FFQ) completed by trained assistants. This semi-quantitative FFQ covered 168 food items frequently consumed by Iranians. All reported consumed foods were converted to g/day by using household measures. The nutrient content of foods was calculated by Nutritionist IV software (N-Squared Computing, Salem, OR). Subjects who reported <800 or >4200 kcal/d were excluded.

*Low protein diet score:* Total protein intake was calculated by summing protein content of all consumed foods. The amount of protein intake for each individual was converted to gram per kilogram body weight (g/kg). As previous study used different amounts of dietary protein for patients with renal disease (17), LPDS was defined based on the 3 cut of points: >2gr/kg (score=1), 1.01-2 gr/kg (score=2), ≤ 1gr/kg (score=3).

For example, a patient who consumed 1.5gr/kg received a score of 2.

*Biochemical measures:* After 12-hour overnight fasting, a blood specimen was collected. Then samples were centrifuged at 3000×g for 10 min. The concentration of blood urea nitrogen (BUN) was measured by using urease enzyme. We assessed the concentration of serum creatinine (SCr) by standard spectrophotometric. Fasting blood sugar (FBS), triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high sensitivity C-reactive protein (hs-CRP) were measured as cardiometabolic variables. The level of FBS, TG and TC was analyzed by using enzymatic colorimetric tests. LDL-C concentration was measured by blocking and then enzymatic methods. Immunoturbidimetry assay was run to determine the level of hs-CRP. All kits were produced by Pars Azmoon Inc.

*Other variables:* General characteristics of patients were asked by oral questions. Socioeconomic status was evaluated by questions regarding income, occupation, education and region of residence. Physical activity was assessed by a one-day physical activity record.

*Statistical Analysis:* Normal distribution of variables were tested by Kolmogorov-smirnov test and checking the histogram curve. Qualitative variables included CKD stage, physical activity level (low, moderate and high), marital status, sex ratio and socioeconomic status (low, moderate and high) were presented as percentage frequency. Difference in these variables was assessed by Chi-square test. Quantitative variable (age, body mass index, biomarkers and dietary intakes of nutrients) reported as mean ± standard deviation. Biochemical variables were compared across the LPDS by analysis of variance (ANOVA). We used analysis of covariance (ANCOVA) to report energy-adjusted nutrient intakes across the scores of a low protein diet. Odds ratio and 95% confidence interval of CKD progression was calculated by logistic regression. The risk of being in the higher stage of CKD was presented in crude and 3 adjusted models. The firs model was adjusted for age, physical activity and body mass index. Further adjustment was performed for systolic blood pressure and diastolic blood pressure in model 2. The intake of carbohydrate, fat, potassium and phosphorus was included in the third model. We considered $P<0.05$ as significance level. Also, we used SPSS version 20 (IBM) to analyze this data.

## Results

We have displayed demographic characteristics of the subjects with CKD across LPDS in Table 1. There was no significant difference in the age of subjects across LPDS (P=0.42). The percentage of male in the lower LPDS category was higher (P=0.04). Subjects with top score had higher body mass index (BMI) (P<0.01). We did not observe any significant comparison for other variables.

Energy adjusted dietary intake of selected unfavorable nutrients in renal insufficiency across LPDS is shown in Table 2. Patients who received higher score, consumed lower amounts of cholesterol, saturated fatty acid, phosphorus, potassium and sodium (P<0.01 for all).

Biochemical measurements of subjects with CKD across LPDS are displayed in Table 3. In comparison with the bottom LPDS, a marginally significant lower BUN was observed among subjects with higher score (P=0.06). We did not observe any significant comparison for other variables.

Table 4 shows the risk of CKD progression across LPDS. Odds ratios were reported in 4 different models. We did not observe any significant increased risk of higher stage of CKD in crude model (P for trend=0.84), model 1 (P for trend=0.22) and model 2 (P for trend=0.24). After adjusting for all potential confounders, a significant decreasing trend for risk of higher stage of CKD across LPDS was revealed (P for trend=0.04).

## Discussion

The results of the present study showed that subjects with higher LPDS consumed lower amounts of unfavorable nutrients for subjects with CKD. Also, we found that adherence to a low protein diet could decrease the risk of CKD progression to the higher stage. To the best of our knowledge, this is the first study to introduce LPDS as an index for assessing diet quality and a predictor of CKD progression.

**Table 1.** Demographic characteristics of the subjects with chronic kidney disease across scores of the low protein diet

| Variables | Low protein diet score | | | P value1 |
|---|---|---|---|---|
| | 1 (>2 gr/kg) N=26 | 2 (1.01-2 gr/kg) N=167 | 3 (≤ 1 gr/kg) N=34 | |
| Age (y) | 65.54±10.512 | 65.14±9.23 | 67.53±10.87 | 0.42 |
| Male (%) | 23 | 34 | 53 | 0.04 |
| Socioeconomic status (%) | | | | |
| Low | 15.4 | 9.6 | 8.8 | |
| Moderate | 65.4 | 67 | 55.9 | |
| High | 19.2 | 23.4 | 35.3 | 0.75 |
| Married (%) | 100 | 98.2 | 97.1 | 0.69 |
| Body mass index (kg/m$^2$) | 21.75±3.04 | 23.58±3.34 | 25.64±3.03 | <0.01 |
| Physical activity level (%) | | | | |
| Low | 65.4 | 63.5 | 70.5 | |
| Moderate | 30.8 | 35.3 | 26.5 | |
| High | 3.8 | 1.2 | 2.9 | 0.43 |
| CKD Stage (%) | | | | |
| 3 | 42.3 | 46.7 | 50 | |
| 4 | 57.7 | 53.3 | 50 | 0.84 |

*[1] Calculated by chi-square test (for qualitative variables) or analysis of variance (for quantitative variables)*
*[2] Qualitative and quantitative variables are expressed as percentage and mean±SD, respectively.*

**Table 2.** Energy adjusted dietary intake of selected unfavorable nutrients in renal insufficiency across scores of the low protein diet

| Variables | Low protein diet score | | | P value1 |
|---|---|---|---|---|
| | 1 (>2 gr/kg) N=26 | 2 (1.01-2 gr/kg) N=167 | 3 (≤ 1 gr/kg) N=34 | |
| Cholesterol (mg) | 291.19±70.072 | 192.84±68.11 | 99.77±70.06 | <0.01 |
| Saturated Fatty acid (g) | 33.87±13.97 | 22.73±13.54 | 12.63±13.98 | <0.01 |
| Potassium (mg) | 4930.27±920.14 | 3317.81±893.71 | 1864.53±919.94 | <0.01 |
| Phosphorus (mg) | 2407.77±378.01 | 1549.74±376.13 | 834.20±377.93 | <0.01 |
| Sodium (mg) | 7778.73±4886.06 | 6183.35±6393.47 | 3997.60±2879.23 | <0.01 |
| Magnesium (mg) | 443.89±79.61 | 313.81±77.27 | 171.51±79.63 | <0.01 |

*[1] Calculated by analysis of covariance*
*[2] Mean±SD. All values are adjusted for total calorie intake except for energy intake.*

We observed an increased intake of sodium, phosphorus and potassium across LPDS. Legumes, meats and dairy are important sources of dietary protein. Legumes are rich in potassium and phosphorus (18). Moreover, previous studies reported an animal based diet resulted in higher sodium and phosphorus intake (19, 20). Also, vegetables (e.g., carrots, tomatoes, potatoes and stewed leafy vegetables) are consumed along with meats and legumes in Iran. Therefore, we observed higher potassium intake among those with higher protein intake. Usual diet quality indices focus on higher intakes of fruits, vegetables, legumes, whole grains and low-fat dairy (8). Therefore, we cannot use these diet indices to evaluate the quality of diet in patients with CKD because adherence to these recommendations results in higher intake of potassium, phosphorus

**Table 3.** Biochemical measurements of subjects with chronic kidney disease across the low protein diet score

| Variables | Low protein diet score | | | P value1 |
|---|---|---|---|---|
| | 1 (>2 gr/kg) N=26 | 2 (1.01-2 gr/kg) N=167 | 3 (≤ 1 gr/kg) N=34 | |
| BUN (mg/dl) | 20.08±2.302 | 19.40±2.73 | 18.50±2.54 | 0.06 |
| Creatinine (mg/dl) | 1.91±0.28 | 1.97±0.24 | 1.96±0.29 | 0.52 |
| GFR (mL/min/1.73m2)3 | 22.93±6.05 | 29.59±6.04 | 31.28±7.72 | 0.36 |
| Total cholesterol (mg/dl) | 271.73±24.68 | 271.13±21.79 | 272.32±17.45 | 0.95 |
| Triglyceride (mg/dl) | 246.92±32.75 | 253.17±29.91 | 253.15±29.81 | 0.61 |
| LDL (mg/dl) | 133.50±18.98 | 133.35±20.21 | 138.65±24.99 | 0.40 |
| FBS (mg/dl) | 130.58±14.76 | 129.20±14.44 | 129.79±13.49 | 0.89 |
| hs-CRP (mg/L) | 1.65±0.31 | 1.60±0.32 | 1.60±0.31 | 0.82 |

*BUN: blood urea nitrogen, FBS: fasting blood sugar, GFR: glomerular filtration rate, hs-CRP: high sensitivity reactive protein, LDL: low density lipoprotein*

*[1] Calculated by analysis of variance; [2] mean±SD; [3] Calculated by MDRD equation*

**Table 4.** Odds ratio (95% CI) for higher stage of chronic kidney disease across scores of the low protein diet

| Variables | Low protein diet score | | | P value1 |
|---|---|---|---|---|
| | 1 (>2 gr/kg) N=26 | 2 (1.01-2 gr/kg) N=167 | 3 (≤ 1 gr/kg) N=34 | |
| Crude | 1 (Ref) | 0.84 (0.36, 1.93) | 0.73 (0.26, 2.05) | 0.84 |
| Model 1 | 1 (Ref) | 0.67 (0.27, 1.71) | 0.36 (0.11, 1.20) | 0.22 |
| Model 2 | 1 (Ref) | 0.66 (0.26, 1.68) | 0.37 (0.11, 1.23) | 0.24 |
| Model 3 | 1 (Ref) | 0.39 (0.12, 1.30) | 0.11 (0.02, 0.66) | 0.04 |

*Model 1: adjusted for age, physical activity and body mass index*
*Model 2: model 1 + systolic and diastolic blood pressure*
*Model 3: model 2 + dietary carbohydrate, fat, potassium and phosphorus*

and protein intake. In contrast, our findings revealed that LPDS had a favorable association with important nutrients in CKD (protein, sodium, phosphorus and potassium) and it could be used as a diet quality index among patients with CKD.

We did not observe any significant comparison for biochemical variables (LDL, TG, TC, FBS and hs-CRP) except for BUN. It seems that these are more sensitive to the source of protein than its amount. Nutritional guidelines suggested lower red meat consumption to achieve reduction in LDL (21). Previous studies reported that higher red meat intake may be related to increased hs-CRP and TG (22, 23). In contrast, several studies reported that consumption of legumes have a beneficial effect on concentration of inflammatory markers and cholesterol (24, 25). In the designing of LPDS, we did not include the source of dietary protein and it may be the possible reason for non-significant observed result.

Although we did not find statistically significant odds ratio for higher stage of CKD in crude model, multivariate adjusted model (adjusted for dietary factors) showed a significant decreasing trend for risk of higher stage of CKD across LPDS. It shows that dietary factors had a confounding role in the association between LPDS and risk of higher stage of CKD. We did not include sex in multivariate adjusted model because it had been considered in MDRD equation (15). Biochemistrists suggested that adherence to a low protein diet could decrease the amounts of toxic waste products of protein metabolism not excreted due to insufficient renal function (26). Higher protein in-

take results in hyperfiltration, increased acid load and proteinuria (27). These factors may lead to CKD progression (27).

The source of dietary protein was not included in introducing the score and it was the most important limitation of this study. Our previous studies showed that soy as a source of dietary protein may have beneficial effect on metabolic factors in patients with renal diseases (28-31). Therefore, the source of dietary protein should be included in future researches. The design of the present study was cross-sectional and this dietary scoring method should be evaluated in prospective cohort studies. Also we did not measure other renal biochemical variables such as proteinuria and urine creatinine in this study.

We introduced a novel index of diet quality for patients with CKD and it was the major strength of the present study. As dietary recommendations for management of CKD emphasize on lower intake of fruits, vegetables, legumes, dairies and whole grains (32) we cannot assess diet quality of these patients by usual diet quality indices (e.g., HEI-2010 and DQIs). Therefore, the results of this study introduce a good diet quality index to evaluated quality of diet of individuals with CKD. Also, we measured cardiometabolic biochemical variables (i.e., LDL, TG, TG, FBS and hs-CRP) because their abnormal levels were prevalent among these patients (28, 30)

In conclusion, the results of the present study showed that higher LPDS was associated with favorable nutrients intake (lower intakes of sodium, potassium, phosphorus, cholesterol and saturated fatty acid) among patients with CKD. Moreover, subjects who received higher LPDS had a marginally significant lower BUN. Also, we observed that LPDS was inversely related to the risk of being in the higher stage of CKD after adjusting for potential confounders. Therefore, it was a predictor of CKD progression.

The results of the present study showed that subjects with higher LPDS consumed lower amounts of unfavorable nutrients for subjects with CKD. Also, we found that adherence to a low protein diet could decrease the risk of CKD progression to the higher stage.

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