Lactulose for Reduction of Nitrogen Products in Patients With Chronic Kidney Disease

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Introduction. Patients with chronic kidney disease (CKD) face with uremic toxins. Lactulose could reduce serum urea and creatinine levels and have some effects on lipid profile and bone minerals. The aim of this study was to evaluate effect of lactulose on serum levels of biochemical products in patients with CKD.
Materials and Methods. In this prospective study, 40 patients with stages 3 and 4 of CKD (52.5% men; mean age, 57.5 ± 12.5 years) were evaluated. All patients received lactulose, 30 mL, 3 times per day for 2 months. Blood samples from all participants were collected before and at the end of intervention to examine changes in biochemical parameters, including sodium, potassium, hemoglobin, urea, creatinine, uric acid, leukocyte and platelets count, β2-microglobin, and intact parathyroid hormone.
Results. Lactulose significantly decreased urea levels from 70.35 ± 28.00 mg/dL to 64.50 ± 23.51 mg/dL (P = .04), creatinine levels from 4.04 ± 1.78 mg/dL to 3.45 ± 1.39 mg/dL (P < .001), uric acid levels from 7.31 ± 1.49 mg/dL to 6.71 ± 1.42 mg/dL (P < .001), and β2-microglobin levels from 3.25 ± 0.44 mg/L to 3.08 ± 0.33 mg/L (P = .001). The decrease in serum electrolytes, lipid profile, and intact parathyroid hormone levels were not significant.
Conclusions. Lactulose administration in CKD patients could decrease levels of various deleterious elements, especially nitrogen products, and its daily use can be recommended in these patients.

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INTRODUCTION

In the past decades, considerable efforts have been directed at improving human (as well as animal) health or preventing disease by the use of functional foods to which prebiotics and probiotics belong.[1,2] Numerous scientists investigated the health-promoting effect of prebiotics like indigestible sugars, eg, fructooligosaccharides, inulin, and lactulose.[3,4] The positive effects of lactulose on colonic metabolism in human is well known.[5] Lactulose is a commercially available disaccharide that is used as a drug in the treatment of hepatic encephalopathy and chronic constipation,[6,7] which has been shown to stimulate the growth of bifidobacteria.[8] There are also reported effects of prebiotics like lactulose on lipid profile and some other biomarkers in normal subjects.[9-13]

In patients with chronic kidney disease (CKD), potentially toxic compounds are accumulated in the body, called uremic toxins,[14] among these some could easily excreted by kidney, but some have low excretion. All efforts are due to reduce these products. In chronic kidney failure, lactulose could promote fecal excretion of water, sodium, potassium, ammonium, urea, creatinine, and protons.[15] Lactulose, as a prebiotic, plays an

important role in regulating nitrogen unwanted products and biochemical parameters in healthy individuals, but there is little information about these effects on patients with kidney failure. In this study, we aimed to evaluate effects of lactulose on serum levels of various biochemical parameters of patients with CKD.

MATERIALS AND METHODS

In this prospective before-after intervention study, 40 patients with CKD in the stages 3 and 4 were evaluated. Patients with at least 1 year of CKD diagnosis were included. Patients older than 18 years with an estimated glomerular filtration rate (GFR) of 60 mL/min/1.73 m^2 and less were included in the study. The exclusion criteria were a history of gastrointestinal or metabolic disease, previous surgery (apart from appendectomy), antibiotic treatment or any other medical treatment influencing intestinal microbiota (especially probiotics, prebiotics, and symbiotics) during the 3 months before the start of the study. Participants were advised to maintain their usual diet during the study period and to avoid intake of fermented milk products and food components containing high quantities of fermentable carbohydrates. Those who could not keep up with the study protocol or tolerate study medications were excluded. The participants did not have to restrict their everyday diet, medication, or daily activities. The Ethics Committee of the Tabriz University of Medical Sciences approved the study, and all patients gave informed consent.

The study was conducted over an 8-week period. The participants received 30 mL of lactulose syrup (Ramopharmin Co, Tehran, Iran), 3 times a day. The doses administered were chosen based on therapeutic recommendations for CKD patients in a way that they would not suffer from negative effects or discomfort. Before and at the end of the study, blood samples were collected. Blood concentrations of nitrogen waste products were measured before and after lactulose treatment, including urea, creatinine, β2-microglobulin, and uric acid, as well as biochemical parameters including hemoglobin, leukocyte and platelet count, calcium, phosphate, and intact parathyroid hormone levels. Liver function tests (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) and serum albumin levels were also measured. Biochemical parameters concentrations were measured using standard laboratory techniques. Serum β2-microglobulin and intact parathyroid hormone concentrations were measured using enzyme-linked immunosorbent assay. All serum biomarkers were carried out in one laboratory. Estimated GFR was calculated by measuring the serum creatinine and applying the Cockcroft-Gault formula.

Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). Continuous variables were expressed as mean ± standard deviation. Differences in the means before and after treatment were evaluated by the paired sample *t* test. A *P* value less than .05 was considered significant.

RESULTS

Forty CKD patients, including 21 men (52.5%) and 19 women (47.5%) with a mean age of 57.5 ± 12.5 years (range, 34 to 87 years) were evaluated. Their

Table 1. Mean Laboratory Values Before and After Treatment With Lactulose in Patients With Chronic Kidney Disease

Parameter	Before Treatment	After Treatment	*P*
Hemoglobin, mg/dL	11.26 ± 1.92	11.12 ± 1.70	.47
Leukocyte count, × 10^9/L	6.84 ± 2.07	7.07 ± 1.50	.35
Platelet count, × 10^9/L	211.22 ± 71.73	222.45 ± 70.10	.24
Triglyceride, mg/dL	139.90 ± 58.65	133.70 ± 53.48	.24
Cholesterol, mg/dL	176.70 ± 45.94	171.45 ± 43.71	.12
Albumin, g/dL	3.30 ± 0.31	3.37 ± 0.42	.33
Calcium, mg/dL	9.35 ± 0.54	9.14 ± 0.47	.06
Phosphorus, mg/dL	4.88 ± 1.51	4.75 ± 1.06	.44
Intact parathyroid hormone, pg/mL	293.32 ± 66.01	283.25 ± 60.15	.06
Alkaline phosphatase, U/L	219.32 ± 82.46	217.12 ± 85.91	.86
Aspartate aminotransferase, U/L	17.20 ± 5.60	16.80 ± 4.35	.51
Alanine aminotransferase, U/L	16.60 ± 3.81	16.93 ± 3.64	.46

Table 2. Mean Changes in Levels of Blood Nitrogen Products After Treatment With Lactulose in Patients With Chronic Kidney Disease

Parameter	Before Treatment	After Treatment	*P*
Creatinine, mg/dL	4.04 ± 1.78	3.45 ± 1.39	< .001
Urea, mg/dL	70.35 ± 28.00	64.50 ± 23.54	.04
Uric acid, mg/dL	7.31 ± 1.49	6.71 ± 1.42	< .001
β2-microglobulin, mg/L	3.25 ± 0.44	3.08 ± 0.33	< .001

GFR was 28.7 ± 14.2 mL/min/1.73 m^2. The etiology of CKD disease was diabetes mellitus in 8 patients, hypertension in 10, glomerulonephritis in 6, polycystic kidney disease in 4, and unknown in 12.

Laboratory findings before and after treatment are shown in Table 1. Although there was a decrease in lipid profile and intact parathyroid hormone levels, the difference was not significant. Serum creatinine, urea, and acid uric levels were significantly reduced after the treatment with lactulose (Table 2). Serum levels of β2-microglobulin were also significantly lower at the end of study when compared with the values before the study.

DISCUSSION

During the progress of CKD, most unwanted products that used to be excreted or metabolized by the kidney are accumulated in the body. These products could have deleterious effects and are known as uremic toxins.[9,16] Low molecular weight products soluble in the water like creatinine and urea could be excreted during the dialysis, but middle molecular weight products (β2-microglobulin) protein bond toxins (p-cresol) have low clearance and are not properly excreted.[17]

Prebiotics like fructooligosaccharides are shown to be useful in the nitrogen excretion through digestive route and help kidney function, especially in kidney failure cases.[18] Prebiotics tolerability and effectiveness are shown in CKD patients.[19] Although lactulose adherence is relatively poor, in large part due to gastrointestinal adverse effects such as abdominal pain, bloating, and flatus,[20-23] it is well tolerated in CKD patients,[19] and this is possible that lactulose as a prebiotic could be helpful in non-renal excretion of these nitrogen products. In this study we evaluated this possibility in patients with advanced CKD. We only evaluated low- and middle-weight products and observed a significant reduction after 2 months of treatment with oral lactulose. As 1 month before and during the study period, all patients were on routine medical management with the same quantity and quality, these reductions could be attributed to lactulose administration. This reduction is possibly due to increased fecal excretion of nitrogen products and reduced urinary excretion.[24] It is shown that lactulose causes a reduction in urea production in patients with hepatic encephalopathy,[25] and increases nitrogen excretion into the fecal fractions in cirrhotic patients.[26]

A systematic review and meta-analysis by Rossi and colleagues[27] showed that using prebiotics and probiotics, including lactulose, could reduce protein-bound uremic toxins, including p-cresyl sulphate and indoxyl sulphate (that are not properly filtered from kidney), in CKD patients. However, we evaluated only urea, creatinine, and β2-microglobulin. Combining the systematic review article[27] with our findings, it could be concluded that prebiotics, including lactulose, have significant effects on reducing uremic toxins in CKD patients.

In this study, we also observed nonsignificant improvement in non-nitrogen biochemical parameters, including lipid profile and blood parameters. We could not specify the exact mechanism by which lactulose would have caused these changes; however, these changes could be due to medical treatments like erythropoietin and phosphate binders, which are routinely given to all CKD patients.

Various findings on lipid profile are reported concerning prebiotics use. In the studies of prebiotics on rats, a significant decrease in serum triglyceride levels is reported.[28-30] A decrease in cholesterol levels is also reported.[28] However, it is reported that lactulose may raise serum cholesterol levels.[31] Studies on humans are scarce. The data on human subjects with hypercholesterolemia indicate that inulin (a nondigestable sacharide) may lower both serum total and low-density lipoprotein cholesterol.[9] In the study of Vogt and colleagues on healthy humans,[10] they only observed triglyceride lowering effects of lactulose, and no effect on cholesterol. However, still there is no exact explanation of mechanism of these effects.

There is a direct relation between calcium and phosphorus levels with parathyroid hormone; in our study, calcium and phosphorus did not have significant reduction, which could be an explanation for nonsignificant reduction of intact parathyroid hormone in our study. Several studies have investigated the effect of prebiotics on mineral (eg, calcium, magnesium, and phosphate) absorption in humans; the results were controversial, as some reported no significant effect,[32,33] and some (especially those with lactulose use) reported stimulation of calcium absorption.[11-13] However, in our study, we found no significant reduction in blood levels of calcium after treatment with lactulose. Like our findings, Teuri and colleagues[34] did not report any effect of inulin (as a prebiotic) on circulating parathyroid hormone and ionized calcium in healthy humans. However, all these findings are in healthy subjects and we did not observe any effect of lactulose on parameters like parathyroid hormone, calcium, and phosphorus.

We did not evaluate lactulose effect on protein-bound products like p-cresol and indoxyl sulphate that are not properly filtered from kidney; this could be a limitation to our study. Another limitation of our study is having no control group and short period of study. As another limitation, we could not control patients' food and life style during the study, which could affect the blood urea nitrogen levels. The longer treatment with lactulose would show better results or vice versa.

CONCLUSIONS

Lactulose administration in CKD patients along with other treatments has beneficiary effects of reduction of some nitrogen products. In addition, there is a possibility of its positive effects on some other parameters, especially parathyroid hormone, calcium, and phosphorus levels. The use of lactulose in CKD patients can be suggested in order to receive better therapeutic results. More studies are needed to confirm these findings.

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CONFLICTS OF INTEREST

None declared.

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