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Original Scientific Paper

PROBIOTICS AND HIGH FIBER-RICH DIETS HAVE ANTI-INFLAMMATORY PROPERTIES AND DECLINE CHRONIC KIDNEY DISEASE PROGRESSION

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SUMMARY – A well balanced, time-restricted diet with 50% more vegetables and restriction of red meat can delay the progression of kidney damage. This paper suggests that such diet changes can also have an immunoregulatory role, with adding pre/probiotics. There were two groups of patients (20M/28F; age 67±9 years, estimated glomerular filtration rate 42,1±12 ml/min/1.73m^2): group A practiced a modified diet that consisted of certain nutritional changes (50% more vegetable intake, reduction of red meat to twice per week), time-restricted eating (8 hours), and taking probiotics. Group B was also taking probiotics; however, their nutrition included no restrictions on red meat intake, they ate fewer vegetables, and there was no time-restricted eating.

After 3 months, therapy from Group A – a balanced, time-restricted diet plus probiotics, resulted in weight loss (from 113±13 to 110±18 kg), body mass index decrease (from 36.4±5.1 to 34±5 kg/m^2), decrease in waist circumference (from 119±11 to 115±10 cm), as well as lower hsC-reactive protein by 8% (group A) and 5% (group B). The values of kidney function measurements after 3 months were 45,3±11 ml/min/1.73m^2 in group A, while in group B, those were 42,4±10 ml/min/1.73m^2 ($p<0.05$). This study shows a positive correlation between the daily consumption of probiotics and decreased progression of chronic kidney disease.

Key words: *probiotics, fiber-rich diets, chronic kidney disease*

Introduction

An imbalance of intestinal microflora and the destruction of the intestinal barrier function can enhance the occurrence and progression of chronic kidney damage. Chronic kidney disease (CKD) related dysbiosis and changes in the intestinal barrier lead to inflammation with an increased translocation of living bacteria products from the intestinal lumen into the circulation[1]. In CKD, dysbiotic intestinal microflora has been reported with an increase in pathogenic compared to symbiotic flora[1,2]. The intestinal microflora produces indoles, phenols, and amines, that are absorbed and accumulated in CKD patients, with harmful effects. These gut-derived uraemic toxins and the increased permeability of the intestinal barrier in CKD patients cause increased inflammation and oxidative

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stress, cardiovascular disease, anaemia, mineral metabolism disorders, and CKD progression[2]. The interaction between the intestinal microbiota and the kidney is known as the 'gut–kidney axis'[3]. The high concentration of ammonia results in lower pH in the gastrointestinal tract, prolonged colonic transit, and dietary restrictions leading to decreased fibre intake [4]. The pathophysiology of chronic inflammation in CKD is the consequence of many factors such as cellular – oxidative stress, tissue – hypoxia, microbial factors – gut dysbiosis, and retention of uraemic toxins (glycation end products, calcioprotein, indoxyl sulphate) [3]. The intake of prebiotics and probiotics could lead to an improvement of the dysbiosis and/or an increase of permeability of the intestinal barrier in many conditions and diseases[5].

As stated, by adding 50% more vegetables to the diet and reducing red meat intake, and with 8-hour fasting, the progression of chronic kidney disease and damage in a terminal stage can be delayed[6]. We also suggest a potential immunoregulatory role of diet changes and adding pre/probiotics (inulin/bifidobacteria and lactobacilli) in CKD patients with estimated glomerular filtration rate (eGFR) >30 ml/min/1.73m^2.

Subjects, materials, and methods

This study included 48 non-dialysis CKD patients (20M/28F; average age 67±9 years, average eGFR 42,1±12 ml/min/1.73m^2.) with no medical history of any gastrointestinal inflammation disease, disorders of liver function, or diabetes. Exclusion criteria were therapy with potassium and phosphate binders, antibiotics, oral iron, oral anticoagulation therapy (OACs) and proton pump inhibitors; conditions like CKD stage 4 and 5, kidney transplantation, heart failure, anemia, malnutrition or inflammation (measured with C-reactive protein or hs CRP>5mg/l). There were two groups of patients: group A had a modified diet that consisted of certain nutritional changes (50% more vegetable intake, reduction of red meat intake to twice per week), time-restricted eating (8 hours), and taking probiotics (inulin/bifidobacteria and lactobacilli twice daily). Group B was also taking probiotics, but their nutrition included no restrictions on red meat intake, they ate fewer vegetables, and there was no time-restricted eating. A food frequency survey was used to collect information on food consumption at home, as well as the number of servings (<3, >3), like in previous study [6]. There were no differences in kidney function, cholesterol, serum albumin, age, sex, fasting glucose, duration, and hypertension therapy between groups and constipation. Constipation was defined as a digestive system condition where an individual has hard feces difficult to expel (Y or N) [7]. We also evaluated the hyperkalaemia risk of increased intake of fruits and vegetables and measured hsC-reactive protein (CRP) before and after 3 months of stated therapy to manipulate the microbiota with probiotics.

Patients were taking antihypertensive medications, including angiotensin II receptor blockers or ACE inhibitors, calcium blockers, and diuretics. Their blood pressure was measured twice in the sitting position (with a conical cuff that fits normal and large arms) after a resting period of 10 minutes. Serum creatinine levels data, as well as age, sex, and race were used to calculate the estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[8]. The protocol of this study follows the Declaration of Helsinki, as well as local institutional guidelines, and it was approved by the local ethics committees.

Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage. The level of statistical significance was chosen to α=0.05. Statistical analysis was performed by statistical package SPSS, version 17.0 for Windows.

Results

Table 1. shows the study subjects' characteristics. Our primary goal was to evaluate the efficacy and safety of reduced intake of red meat (twice per week), increased vegetable intake (50% more), plus probiotics, and a time-restricted diet (min. 8-hour fasting) in 48 CKD patients with eGFR>30ml/min/1.73m^2. There were no statistically significant differences between laboratory values in groups of patients stratified according to the primary kidney disease, age, and sex. HsC-reactive protein was measured before and after 3 months of therapy to manipulate the microbiota with probiotics and diet. In group A, the treatment that included diet changes plus probiotics after 3 months resulted in body mass index decrease (BMI) from 36.4±5.1 to 34±5 kg/m^2, weight loss from 113±13 to 110±18 kg, and in a decrease of waist circumference

Table 1.: Patients characteristics (clinical and metabolic)

Gender	20/28 (M/F)
Age	67 (58-76)
CKD (duration in years)	9 (7-12)
BMI (kg/m2)	36.4 ±5.1
SBP (mmHg)	145 (130-160)
DBP (mmHg)	82 (63-101)
hs CRP (mg/L)	3.4±1.5
Serum albumine (g/L)	38.1±2.3
Fasting glucose (mmol/L)	5.4±1.2
Total cholesterol (mmol/L)	5.4 (3.6-6.8)
Potassium (mmol/L)	4.4±0.5
Creatinine (umol/L)	152 (138-175)
eGFR (ml/min/1.73m2)	42.1 (31-55)

BMI – index of body mass; SBP/DBP – systolic/diastolic blood pressure; hs CRP – high sensitive C reactive protein; eGFR – estimated glomerular filtration rate

from 119±11 to 115±10 cm. Kidney function measured with eGFR after 3 months in group A increased to 45,3±11 ml/min/1.73m^2, while in group B, it was 42,4±10 ml/min/1.73m^2($p<0.05$). Furthermore, in group A the 3-month administration of diet plus probiotics caused decrease in systolic BP (SBP from 145±15 to 140±12 mmHg ($p<0.05$). On the other side, their diastolic BP (DBP from 82±19 to 78±16 mmHg ($p=0.9$)) and heart rate (HR from 78±10 to 75±11 beats/min ($p=0.01$)) did not significantly change.

Group B showed no changes in BMI (from 36.4±5.1 to 36.4±4.5), waist circumference (from 119±11 to 118±13 cm), nor in eGFR (from 42,1±12 ml/min/1.73m^2 to 42.4±10 ml/min/1.73m^2, $p=0.01$). Also, during this 3-months study period, there was no significant decrease in BP (SBP from 145±15 to 144±11 mmHg, DBP from 82±19 to 81±6 mmHg ($p=0.01$)) and HR (from 79±10 to 76±10 beats/min ($p=0.9$)). HsC-reactive protein value decreased in both groups – 8% in group A and 5% in group B. The food frequency survey with data on food consumption at home and the number of servings consumed has shown that 84% of patients in group A have >3 consumption/day, while in group B, there were 65% of patients with less than <3 consumption/day. In group B, the mean eGFR after 3 months was lower than in group A, and it was statistically significant ($p<0.05$). During this study, the patients did not incur any adverse event like hyper- or hypotensive episode, acidosis, or potassium>5.1 mmol/L. At the end of the study, only 13% of patients in group A had problems with constipation (answer Y), while the great majority (answer N) of 87% had no constipation problems. On the other hand, 70% of patients in group B had problems with constipation ($p<0.05$).

A clinical follow-up after 3 months was performed. No one from group A patients has had a worsening of kidney function after the end of the study, and 50% of them were still following a similar diet with less red meat, more vegetables and high-fiber foods and probiotics.

Discussion

There has been significant progress in the prevention, detection, and treatment of CKD, but the fact is that it still remains a significant public health problem[2]. Therefore, it is necessary to develop new approaches to treat CKD patients [6,7]. New evidence has shown that the intestinal microbiota can affect arterial blood pressure and hypertension may therefore be another gut dysbiosis mediated cause of kidney disease[9]. This study showed that BP control is better in both groups by adding probiotics to the daily diet. Also, reducing red meat intake to 2x weekly and increased intake of vegetables (50% more), with time-restricted feeding (8-hour fasting), can slow down and delay the chronic kidney disease progression and could clearly benefit the CKD patients[6]. Our results in this new study support these previous observations and indicate that probiotics and high fiber-rich diets have additional anti-inflammatory properties and can decline CKD progression[10]. Some medications (potassium and phosphate binders, proton pump inhibitors, oral iron, and antibiotics) may underlie a changed composition of the intestinal microbiota in uraemic patients[11]. So patients taking such medications were excluded from the study. The daily diet is crucial and different polyphenols, such as anthocyanin, catechin, chlorogenic acid, and resveratrol, can regulate intestinal microorganisms, inhibit pathogenic bacteria, and improve inflammation in CKD patients[12].

The present study includes potential limitations. First, there was a small number of participants. Second, microbiota, phosphate load, and oxidative stress were not measured. Third, our evaluations were based on measuring the serum creatinine, eGFR and hsCRP

on two consecutive periods before and after 3 months, so it may not reflect the relation over time.

To conclude, the results of this study suggest a positive correlation between daily probiotics consumption and decreased progression of CKD (in both groups). Therapies that include a high fiber diet and probiotics may enhance the well-being of CKD by attenuating uremia-induced alteration of the gut microbiome. The plant-based nutrition with additional pre/probiotics consumption should be implemented as a new approach to CKD patients and included as a clinical recommendation for their treatment.

The Authors declare that this manuscript has not been published previously, nor is it currently being assessed for publication by any journal other than the *Acta Clinica Croatica*. The authors disclose that they did not receive any financial support for the study and that there is no proprietary interest involved in this study.

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Sažetak

PROBIOTICI I DIJETALNA PREHRANA BOGATA VLAKNIMA UZ PROTUUPALNE UČINKE USPORAVA I PROGRESIJU KRONIČNE BUBREŽNE BOLESTI

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Istražili smo učinak dodatka probiotika i njegovu potencijalnu imunoregulatornu ulogu u 48 bolesnika s kroničnom bubrežnom bolesti kroz 3 mjeseca. U prospektivnoj studiji (20M/28F; srednje dobi 67±9 godina, eGFR 42,1±12 $mlmin^{-1}1.73m^{2.}$) bolesnici su bili podijeljeni u skupinu A s dijetom koja je uključivala smanjeno uzimanje crvenog mesa (samo 2x tjedno), povećan unos povrća na 50%, uz 8-satni vremenski period bez uzimanja hrane i uz dodatak probiotika. Skupina B nije mijenjala postojeće prehrambene navike, međutim uzimala je isti probiotik kao i skupina A. U periodu praćenja nakon 3 mjeseca postignuta je značajno sniženje tlaka, težine i opsega struka u grupi A: BMI s 36.4±5.1 na 34±5 kg/m^2, tjelesna težina s 113±13 na 110±18 kg, opseg struka s 119±11 na 115±10 cm, dok u skupini B nisu zabilježene promjene. U obje grupe uočeno je sniženje razine hsCRP-a, i to za 8% u grupi A, odnosno 5% u grupi B.

Bubrežna funkcija procijenjena eGFR nakon 3 mjeseca u skupini A iznosila je 45.3±11 $ml/min/1.73m^2$, a u grupi B 42.4±10 $ml/min/1.73m^2$ ($p<0.05$). Prehrana sa sniženim unosom proteina životinjskog porijekla, više proteina biljnog porijekla, pridržavanje neuzimanja hrane kroz osam sati i dodatak probiotika, dodatno usporava progresiju kronične bubrežne bolesti i ima protuupalni učinak.

Ključne riječi: *probiotici, dijetalna prehrana bogata vlaknima, kronična bubrežna bolest*