INGESTION OF RED MEAT PROMOTES CHRONIC KIDNEY DISEASE PROGRESSION

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Reducing protein intake in patients with chronic kidney disease (CKD) can delay progression in terminal stage. There is strong evidence supporting positive effects of replacing red meat protein with other sources of protein. In this study, the impact of replacing red meat protein was investigated in 46 non-dialysis CKD (ND-CKD) patients with resistant hypertension and followed-up for 6 months (19M/27F; mean age 66±9 years, mean eGFR: (43±12) mLmin-11.73 m^2.). Patients were divided into two groups: group A was put on a special diet (reduction of red meat intake to 2x weekly and adding 50% more vegetables to the diet with 8-hour time restricted feeding); group B had no reduction of red meat intake alongside consuming less vegetable and without time restricted feeding. A food frequency questionnaire was used to collect information on consumption of foods and number of servings consumed. Patients were evaluated at the beginning and after 6 months of management. Specialized diet caused a decrease in body mass index (from 36.4±5.1 kg/m^2 to 33±5 kg/m^2), body weight (from 112±13 kg to 106±18 kg), and waist circumference (from 119±11 cm to 112±10 cm). Additionally, the 6-month administration of specialized diet caused a significant decrease in the office systolic blood pressure (SBP) from 147±15 mm Hg to 140±12 mm Hg, while reduction in diastolic blood pressure (DBP) from 89±8 mm Hg to 86±6 mm Hg (p=0.1) and heart rate was not significant (from 79±10 to 77±11 beats/min (p=0.9). After 6 months, kidney function measured with eGFR was 45.2±14 mL/min/1.73 m^2 in group A and 41.2±11 mL/min/1.73 m^2 in group B (p<0.05). The findings of this study suggest an association between daily consumption of red meat and the risk of CKD progression. The administration of diet for 6 months can be useful in slowing CKD progression (via interaction with acidification in the kidney), while resulting in significant SBP reduction, possibly via interaction with the autonomic nervous system.

Key words: **nutrition, chronic kidney disease**

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INTRODUCTION

The incidence of chronic kidney disease (CKD) is increasing worldwide, with CKD being a significant health problem associated with high morbidity, mortality and costs. It is known that hypertension control is an important contributing factor in reducing cardiovascular risk and renal disease progression. Reducing protein intake in patients with CKD has a potential to additionally delay progression in terminal stage. There is strong evidence supporting positive effects of replacing red meat protein with other sources of protein (1). The prevalence of type 2 diabetes and metabolic syndrome, alongside hypertension, are the main causes of CKD in Western countries, while being significantly lower in vegetarian populations (2). There is a negative relationship between components of plant-based diets and factors related to CKD progression such as inflammation, uremic toxins, metabolic acidosis, phosphate load, insulin resistance and oxidative stress (2). The pathophysiology of chronic inflammation in CKD is the consequence of a multifactorial etiology. There are interactions of a number of factors in the uremic milieu, e.g., exogenous factors (dialysis membranes, central venous catheters), cellular factors (oxidative stress, cellular senescence), tissue factors (hypoxia, fluid and sodium overload), microbial factors (immune dysfunction, gut dysbiosis), retention of uremic toxins (advanced glycation end products, calciprotein particles and indoxyl sulfate) (3). All of the aforementioned factors interact with comorbidities, superimposed acute illnesses, genetic predisposition and therapeutic interventions. Alterations of the gut microbial flora (dysbiosis) are typically found in patients with CKD. The interplay between the intestinal microbiota and the kidney has been acknowledged under the term 'gut-kidney axis' (3,4). The high concentration of ammonia is responsible for lowering pH in the gastrointestinal tract, which in turn induces prolonged colonic transit and dietary restrictions leading to decreased fiber intake. Some medications such as potassium and phosphate binders, proton pump inhibitors, oral iron and antibiotics may underlie the altered composition of the intestinal microbiota in uremic patients (2). Persistent systemic chronic inflammation in patients with CKD contributes to a number of complications including arteriosclerosis, atherosclerosis, osteoporosis, frailty, malnutrition and protein wasting, metabolic syndrome and diabetes, malignancy and depression (5). Problems associated with low provider and patient awareness of kidney disease limit the adherence to CKD care, negatively affecting health outcomes (6). Mediterranean diet has been proven to prevent cardiovascular disease alongside weight reduction due to its resemblance with diets proven to prevent diabetes (6). Nutrition is a common topic in contemporary everyday clinical medicine, not only in nephrology; however, awareness remains fairly low. Our research investigated the consequences of reducing red meat intake on renal function parameters in CKD patients with estimated glomerular filtration rate (eGFR) >30 mLmin^{-1}1.73 m^2.

PATIENTS AND METHODS

Patients

Patients meeting biochemical criteria for CKD (two estimated glomerular filtration rates <60 mL/min/1.73 m^2 taken >90 days apart) were included. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Blood pressure (BP) was measured twice in the sitting position using a BP Monitor with Stroke Risk Detection (Microlife, with a conical cuff fitting normal and large arms). Resistant hypertension was defined as BP at goal with 4 full-dose drugs. A total of 46 overweight RH ND-CKD patients with mildly or moderately decreased renal function (eGFR <60 mLmin^{-1}1.73 m^2) were included and followed for 6 months (age 66±9 years, 19M/27F, serum creatinine 90±17 μmol/L). Patients were divided into two groups: group A was put on a special diet (reduction of red meat intake to 2x weekly and adding 50% more vegetables to the diet with 8-hour time restricted feeding); group B had no reduction of red meat intake alongside consuming less vegetable and without time restricted feeding. A food frequency questionnaire was used to collect information on the consumption of food at home, as well as the number of servings consumed (<3 or >3). There were no differences in renal function, cholesterol, triglycerides, fasting glucose, age, sex, duration and therapy of hypertension between the groups, and constipation. Constipation was defined as a condition of the digestive system in which an individual has hard feces that is difficult to expel (yes or no). The potential hyperkalemia risk of increasing fruit and vegetable intake in group A was also investigated. Patients were evaluated at the beginning and after 6 months of management.

Exclusion criteria were patients with kidney transplantation and history of any gastrointestinal inflammatory disease, heart failure patients, sign of anemia or inflammation (measured with C-reactive protein (CRP) or highly sensitive CRP (hsCRP) >5 mg/L). Patients taking drugs such as oral anticoagulation therapy (OACs) were excluded (vitamin K antagonists). The eGFR was checked at the beginning and after 6 months in both groups. The study was conducted between January and July 2017. This study was conducted in accordance with the amended Declaration of Helsinki. The study was approved by the hospital Ethics Committee and all participants submitted their informed written consent.

Statistical analysis

Data were processed using the SPSS software. Statistical data analysis was performed using descriptive statistics. Continuous variables were presented as mean and standard deviation. Categorical variables were presented as percentage. Paired sample t-test was applied for comparison of results. The level of statistical significance was set at p<0.05.

RESULTS

A cohort of 46 ND-CKD patients showed that 58.7% of available patients were female (F=27). The majority of patients were in the >55 age group (65%). The primary endpoint was to evaluate the efficacy and safety of twice-a-week red meat intake, while also adding 50% more vegetables to the diet alongside 8-hour time restricted feeding in ND-CKD patients. There were no statistically significant differences in laboratory values between the groups of patients stratified according to primary kidney disease, age and sex. Treatment with a specialized diet (group A, 69% F) caused a decrease in body mass index (BMI) from 36.4±5.1 kg/m^2 to 33±5 kg/m^2, body weight from 112±13 kg to 106±18 kg, and waist circumference from 119±11 cm to 112±10 cm ($p<0.05$). Additionally, the 6-month administration of the specialized diet caused a significant decrease in the office systolic blood pressure (SBP, from 147±15 to 140±12 mm Hg ($p<0.05$). However, diastolic BP (from 89±8 to 86±6 mm Hg) and HR (from 79±10 to 77±11 beats/min ($p=0.9$)) did not change significantly ($p=0.01$)). The 6-month administration of a specialized diet did not cause a decrease of eGFR (from 43±13 mLmin^{-1}1.73 m^2 to 45±14 mLmin^{-1}1.73 m^2 ($p=0.01$).

In group B (69.6% M), eGFR decreased from 43±11 mLmin^{-1}1.73 m^2 to 41.2±13 mLmin^{-1}1.73 m^2 ($p=0.01$), BMI changed from 35.2±4.1 kg/m^2 to 34.8±5.2 kg/m^2, weight from 110±11 kg to 109±13 kg, and waist circumference from 116±12 cm to 115±10 cm. However, during the 6 months of the study, a decrease in BP (SBP, from 146±11 to 144±12 mm Hg and DBP from 86±8 to 85±6 mm Hg ($p=0.01$)) and HR (from 77±11 to 76±10 beats/min ($p=0.9$)) was not found to be significant.

The food frequency questionnaire with information on the consumption of foods at home and the number of servings consumed showed that 80% of group A patients had >3 consumptions/day, whereas in group B there were 70% of patients with <3 consumptions/day. After 6 months, the mean GFR in group A was 45.2±14 mL/min/1.73 m^2, while in group B it was 41.2±11 mL/min/1.73 m^2. The mean eGFR was lower in group B than in group A after 6 months, which was statistically significant ($p<0.05$). During the study, none of the patients suffered adverse events such as hypertensive or hypotensive episode, including acidosis or potassium >5.1 mmol/L.

At the end of the study, answer to the question whether patients had problems with constipation was yes in 14% of group A patients and 75% in group B patients ($p<0.05$).

Clinical follow-up after 2 months revealed that two female patients from group B contracted urinary tract infections, and one group B patient had atrial fibrillation. None of the group A patients had deterioration of kidney function after the end of the study, while 50% of group A patients continued to follow a similar diet with less red meat.

DISCUSSION

For more than a century, quantitative reduction of dietary protein intake has been recognized as a therapeutic option in patients with chronic kidney disease. The relationship between dietary protein sources and the risk of incident kidney disease and its progression has long been neglected. Nearly one half of all deaths from heart disease, stroke, and type 2 diabetes (cardiometabolic deaths) among adults in the United States were found to be associated with suboptimal intake of fruits, vegetables, nuts, seeds, and omega-3 fatty acids (1). Results from different studies confirm a kidney-protective effect of plant-based diets in the primary and secondary prevention of CKD progression (5). Wang *et al.* showed that hsCRP and interleukin-6 levels were significantly higher in patients with bacterial DNA than those without it, and bacterial translocation occurs in patients with final stage chronic kidney disease and is associated with microinflammation (5). Studies have determined the nutritional safety of plant-based diets in CKD patients, despite the combination of a varying dietary protein restriction. As observed in the healthy population, this dietary pattern is associated with a reduced risk of all-cause mortality in patients with kidney disease (6). Accumulation of uremic toxins is associated with an increased risk of CKD progression (7). Some uremic toxins are a result of nutrient processing by gut microbiota and serve as precursors of uremic toxins such as indoxyl sulfate and indole-3 acetic acid, trimethylamine N-oxide (TMAO) and p-cresyl sulfate (7). Increased intake of some nutrients may modify the gut microbiota and increase the number of bacteria that process them to uremic toxins and increased risk of CKD progression. It is an opportunity for therapeutic intervention by modifying the diet, modifying the microbiota, increasing toxin excretion, decreasing uremic toxin production by microbiota and targeting specific uremic toxins. Specific focus will be placed on the decreased availability of bacteria-derived metabolites with nephroprotective potential, such as vitamin K (therapy with warfarin induces deficiency of vitamin K) and butyrate and the cellular and molecular mechanisms linking these uremic toxins and protective factors to kidney diseases (7). This allows the development of novel therapeutic approaches. The US Department of Agriculture (USDA) replaced food pyramids with MyPlate in 2011 (8). The plate is divided into four, roughly equal parts: fruits, vegetable, grains, and proteins. The plate is a reminder of how to eat healthier. Beside the plate is the fifth food group, dairy, positioned as a beverage. Dairy can be cheese, or yogurt, a glass of milk or can be substituted with a fortified soy-based beverage (8). Prebiotics should be an integral part of a healthy diet, and dietary fiber is the best-known prebiotic. Fibers are found in vegetables and fruits, legumes, nuts, as well as whole and fiber-enriched grains, keeping digestion moving, binding cholesterol, and pushing out carcinogens (9). Prebiotics balance the composition and activity of the gut flora to benefit health. The consumption of dietary fiber is linked to improved cardiovascular health, lower body weight and can help with issues of gastrointestinal motility (9). Diets that promote weight loss include increased consumption of vegetables, fruits, and high-fiber, whole-grain foods, increased intake of water; and reduced consumption of dietary sugar and sugar-sweetened beverages. Specific diets include the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean diet, which has been correlated with lower risks of cardiovascular disease, cancers, obesity, diabetes type 2, Parkinson disease/cognitive health and death (4). Dietary management of CKD patients focuses on the quantity of energy and protein with little mention of dietary quality. Dietary patterns that are lower in meat, sodium and refined sugar and more plant-based with a higher content of fiber and grains are more important for chronic disease prevention. The potential hyperkalemia risk of increasing fruit and vegetable intake in diet was not detected. Increase in fiber consumption seen in group A leads to better control of constipation without metabolic acidosis. The specialized diet has favorable effects on systolic blood pressure, obesity, and explains the reduced renal function decline observed in non-dialysis CKD patients adhering to diet with less red meat (twice a week) plus 50% more vegetables and 8-hour time restricted feeding. Nutrition plays a key role in managing patients with kidney disease. Patients with CKD are at a high risk of protein energy wasting (PEW) defined as a condition of undernutrition and increased catabolism. The prevalence of PEW is 15% to 18% in predialysis CKD. Reduction in kidney function is associated with an inflammatory response. Ketoanalog supplemented very low protein diet in predialysis CKD should be considered as one of the main approaches in the management program to prevent malnutrition and slow progression of disease (10).

Research by Gabel *et al*. showed that 12 weeks of time-restricted feeding in which an obese person had 8 hours of unrestricted eating followed by 16 hours of water fasting, resulted in mild calorie restriction and may help with weight loss and blood pressure control (11). In our study, we showed that intermittent fasting could be of benefit to CKD patients. Dietary restriction of protein intake has been proposed as a possible kidney-protective treatment.

Many points still need to be addressed for CKD patients, e.g., which diet should be recommended for patients with kidney disease, and which for CKD patients with prediabetes and diabetes. Can we prevent CKD by means of a diet with replacement of red meat protein? Is there any additive effect of such a diet and exercise in CKD prevention? The plant-based diets should be included as part of the clinical recommendations in predialysis or ND-CKD patients.

LIMITATIONS OF THE STUDY

The limitation of this study was that we had no data on serum albumin and levels of hsCRP in order to conclude about malnutrition and inflammation. Patients in this study did not take Keto/Amino Acid-Supplemented protein-Restricted Diets.

CONCLUSION

The findings of this study suggest there is an association between the consumption of red meat and the risk of progression of CKD. The 6-month administration of the diet proved to be useful in slowing the progression of CKD (*via* interaction with acidification in the kidney), resulting in significant additional reduction in SBP, possibly *via* interaction with the autonomic nervous system. The plant-based diets in the future should be included as part of the recommendations for the prevention and management of CKD in everyday clinical practice.

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SAŽETAK

UZIMANJE HRANE S CRVENIM MESOM UBRZAVA PROGRESIJU KRONIČNE BUBREŽNE BOLESTI

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U prospektivnoj studiji ispitan je utjecaj promjene prehrambenih navika u bolesnika s kroničnom bubrežnom bolesti u preddijaliznoj fazi. U 46 bolesnika s rezistentnom hipertenzijom tijekom 6 mjeseci crveno je meso zamijenjeno drugom vrstom proteina biljnog podrijetla (19 M/27 Ž; srednje dobi 66±9 godina, eGFR 43±12 mL/min-11,73 m^2). Bolesnici su podijeljeni u dvije skupine: skupina A je imala dijetu koja je uključivala redukciju unosa crvenog mesa na samo 2 puta/tjedan, povećan je unos povrća na 50 % više nego prethodno, uz 8-satno razdoblje bez uzimanja hrane. Skupina B nije mijenjala postojeće prehrambene navike. Koristili smo upitnik o broju obroka kao i o vrsti uzimanja proteina. U razdoblju praćenja nije bilo neželjenih događaja, a u skupini A u odnosu na skupinu B postignuta je značajna redukcija tlaka, težine i opsega struka: BMI s 36,4±5,1 na 33±5 kg/m^2, tjelesna težina sa 112±13 na 106±18 kg, opseg struka sa 119±11 na 112±10 cm, sniženje sistoličkog krvnog tlaka sa 147±15 na 140±12 mm Hg ($p<0,05$). Sniženje dijastoličkog tlaka nije bilo statistički značajno (s 89±8 na 86±6 mm Hg ($p=0,1$)) kao ni frekvencije (sa 79±10 na 77±11/min ($p=0,9$)) u objema skupinama. Bubrežna funkcija procijenjena pomoću eGFR nakon 6 mjeseci bila je statistički značajna: u skupini A bila je 45,2±14 mL/min/1,73m^2, a u skupini B 41,2±11 mL/min/1,73m^2 ($p<0,05$). Prehrana sa sniženim unosom proteina životinjskog podrijetla uz dodatak proteina biljnog podrijetla te pridržavanje 8-satnog neuzimanja hrane usporava progresiju kronične bubrežne bolesti u bolesnika u preddijalizi.

Ključne riječi: prehrana, kronična bubrežna bolest