

## Editorial

# Low Protein Brown Rice for Preventing Progression of CKD and DKD to End Stage Renal Failure

Shaw Watanabe, MD, PhD<sup>1,2\*</sup>

<sup>1</sup>Lifescience Promoting Association, Daikyo-cho 25-3-1004, Shinjuku-ku, Tokyo 160-0015, Japan

<sup>2</sup>Asia Pacific Clinical Nutrition Society (APCNS), Department of Food Science and Nutrition, Zhejiang University, 866 Yu-Hang-Tang Road, Hangzhou 310058, China

### \*Corresponding author

Shaw Watanabe, MD, PhD

Lifescience Promoting Association, Daikyo-cho 25-3-1004, Shinjuku-ku, Tokyo 160-0015, Japan; Fax: +81-3-5379-7786; E-mail: [watashaw@lifescience.or.jp](mailto:watashaw@lifescience.or.jp)

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Chronic kidney disease (CKD) is pervasive into aging society, affecting permanent implications on patients' life. Approximately 10% of the global population has CKD, and millions die each year. The prevalence of CKD was high in Latin America, Europe, East Asia and the Middle East, where approximately 12% of the population has CKD.<sup>1</sup> Diabetic kidney disease (DKD) or diabetic nephropathy (DN) is a part of CKD when the patients have diabetes.<sup>2</sup> Both CKD and DKD may progressively fall from a normal estimated glomerular filtration rate (eGFR >90 ml/min/1.73 m<sup>2</sup>) to less than 15, at which point the patient becomes end-stage kidney disease (ESKD). The status of DKD could be estimated by measuring the amount of urinary protein and the serum creatinine, which can be used to calculate the eGFR.

Progression rate of CKD/DKD is recently reported by Warren et al<sup>3</sup> who classified 15,517 participants in the community-based Atherosclerosis Risk in Communities (ARIC) study by diabetes status. They quantified eGFR trajectories at four visits over 26 years. Adjusted mean eGFR decline over the full study period among participants without diabetes was - 1.4 ml/min/1.73 m<sup>2</sup>/year, with undiagnosed diabetes was - 1.8 ml/min/year, and with diagnosed diabetes was - 2.5 ml/min/year.

Over the past 90 years, a protein-restricted diet has been successfully used to treat chronic renal failure. Recently, the treatment of CKD uses an angiotensin converting enzyme inhibitor or angiotensin receptor blocker to dilates the glomerular arteriole for reducing hyperfiltration within the glomerular capillaries. Other classes of diabetes medications, such as GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors, are also thought to slow the progression of diabetic nephropathy.<sup>2,4,5</sup>

However, relatively little is known about the optimal way to coordinate, finance and regulate the care for people with CKD, especially the patients living in inequality present low-and-middle income countries. Furthermore, high cost intervention did not yield expected results. In Japan, J-Doit-3 study, in which 2,542 patients were randomly assigned either to ordinary therapy or intensive therapy with multiple targeting of HbA1c, blood pressure, LDL cholesterol, HDL cholesterol, triacylglycerol, and BMI purposed to suppress these values within the normal range.<sup>6</sup> A primary outcome occurred in 109 patients in the intensive therapy group and in 133 patients in the conventional therapy group (hazard ratio [HR] 0.81, *p*=0.094). Only cerebrovascular events were significantly less frequent in the intensive therapy group (HR 0.42, *p*=0.02), but hypoglycemia occurred in 41.1% patients in the intensive treatment *vs.* 22.3% in the control group.<sup>7</sup> Cost-effectiveness would be a problem.

According to the survey conducted by the Japan Society of Dialysis Medicine, the hemodialysis patients was 324,48, an increase of 6,010 from the previous year in 2013. DKD was the most common, with 118,081 patients, accounting for 38.1% of dialysis patients overall, but DKD in newly started dialysis in the past one year was 15,809, accounting for 43.5% of the new hemodialysis.<sup>8</sup>

Prevention of hemodialysis is very important, both for reducing medical costs and for improving patients' quality of life (QOL). Prevention of hypertension and low protein diet are two major strategies against CKD progression. We have reported in the Saku population-based cohort study, in which the decline of eGFR was 1 ml/min/1.73 m<sup>2</sup>/year by ordinary lifestyle of aging, while it was nearly 5 ml among people whose daily meat consumption was large (2.0 g/kg body weight).<sup>9</sup>

However, the critical dose of protein restriction is still in debate. We define the definition of a low protein diet to be less than 0.5 g/kg body weight from the clinical case study.<sup>10</sup> Our clinical review on 241 CKD patients, with a serum creatinine level greater than 5 mg/dL, eGFR kept to decline within 1.0 ml/min/yr by every 0.2 g/kg body weight reduction of daily protein intake. At serum creatinine level lower than 5 mg/dL, a daily protein intake of 0.5 g/kg body weight could decrease urinary protein approximately 1.1 g/day in a relatively short time span. The survival until ESKD was better by a daily protein intake of 0.3-0.5 g/kg body weight with enough energy source intake, while more than 0.6 g/kg body weight showed the same poor prognosis as control.<sup>11</sup>

Effect of low protein diet on CKD patients are denied by many clinicians based upon the Modification of Diet in Renal Disease (MDRD) study.<sup>12</sup> In that study, 585 patients in group A (GFR 22-55 ml/min/1.73 m<sup>2</sup>) were divided into two sets, one set prescribed a normal protein intake (1.3 g/kg/day) and the other a low protein diet (LPD, 0.6 g/kg/day); the 255 patients in group B (GFR 13-24 ml/min/1.73 m<sup>2</sup>) were divided into an LPD set (0.6 g/kg/day) and very low protein diet (VLPD, 0.28 g/kg/day) set. The VLPD set were prescribed a daily 0.28 g/kg amino acid-keto acid supplement and multivitamin tablet. Energy intake was set at 30 kcal/kg body weight. Follow-up period of 2.2 years on an average and an additional 9-month follow-up showed poor prognosis in the VLPD group. However, the actual protein intake was found to be above the set level, and the energy intake had been low (22-20 kcal/kg), so that the malnutrition would be the cause of death. In our opinion, failure of the MDRD study to demonstrate efficacy of LPD, was mostly explained by insufficient energy intake.<sup>13</sup>

The FROM-J study was introduced with the aim of preventing CKD and reducing the use of hemodialysis by 15% after 5 years.<sup>14</sup> In this study, the set level of low protein diet was 0.8 vs. 1.2 g/kg body weight, so the study could not show the benefit of low protein diet.

We have recommended low protein rice for CKD patients.<sup>15,16</sup> Protein overload promotes glomerular hyperinfiltration which causes profibrotic effects. Excessive renal mTOR activation increases protein synthesis and decreases autophagy. This process may lead to cellular apoptosis to lead ESKD.<sup>17</sup>

At present, a low protein rice has been made from polished white rice, so almost all nutrients except starch were lost.<sup>18</sup> New protein-extracted brown rice is made from wax-free brown rice (WFBR) which makes it possible to immerse proteinase enzyme solution.<sup>19</sup>

Rice protein was extracted 70-75% from brown rice, and ash was also reduced. The remaining minerals were only 0.3% in potassium, 8.4% in magnesium, 9.6% in manganese, 15.7% in phosphate, and 39.5% in zinc. Dietary fibers remained as same as the brown rice, although water-soluble fiber seemed to be more easily solved out than insoluble dietary fiber during cooking. As for the micronutrients, vitamin B1 was remained almost 90% in

WFBR, but vitamin E, niacin, folic acid and pantothenic acid were lost 30 to 40%. The antioxidant activity of both brown rice and WFBR remained 3-4 unit in the boiled rice, mostly water-soluble AOU-L. Polished white rice did not show antioxidant activity at all.

Newly-made protein extracted wax free brown rice (LPBR) could be expected to have wide usage in clinical nutrition.<sup>19</sup> CKD patients have a necessity to reduce phosphorus and potassium intake in addition to decrease protein intake. At the same time, there is a need to ensure the patient takes in enough energy source. LPBR meets all these requirements as a staple food for CKD patients. Additional benefits should be obtained for the disease by dietary fiber, vitamins, gamma oryzanol, ferulic acid and antioxidant activity. Almost no potassium and low phosphate in LPBR were also beneficial for the patients to prevent hyperkalemia and hyperphosphatemia. Dietary fiber intake stimulated the growth of intestinal bacteria which produce short-chain fatty acids, which are beneficial for gut environment.<sup>20,21</sup>

Primary, secondary and tertiary prevention measures exist for CKD, DKD and ESKD. Such measures include public education on healthy dieting, exercise, proper body weight, self-awareness of serum creatinine, urinary albumin and blood pressure levels.<sup>22</sup> A low protein brown rice is a hope of medical rice.<sup>23</sup> A new low protein diet could be developed by using this rice, and it becomes easier to make a recipe more tasteful for the patients with renal failure.

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