Review Article

Dietary therapy with low protein *genmai* (brown rice) to improve the gut-kidney axis and reduce CKD progression

Shaw Watanabe MD, PhD[1], Kyoka Adachi MD[2], Shu Wakino MD, PhD[3], Takahisa Hisada PhD[4], Jun Mochizuki PhD[4]

[1]*Lifescience Research Institute, Tokyo University of Agriculture, Tokyo, Japan*
[2]*Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan*
[3]*Tokushima University, Medical School, Tokushima, Japan*
[4]*Techno-Suruga Laboratory, Shizuoka, Japan*

Low protein rice can be part of a nutritionally adequate dietary pattern in the prevention of chronic kidney disease. We developed a low protein fermented *genmai* (brown rice) LPFG) to improve chronic kidney disease (CKD) management. The principal functional features of brown rice are retained in LPFG, lessening the negative spiral of gut-kidney associative spiral attributable to uremic dysbiosis and a leaky gut. LPFG is characterized by (1) an energy value the same as white rice, (2) a protein content less than 0.2 g/ 100 g, (3) a potassium content almost zero, (4) phosphorus less than a quarter that of conventional rice, (5) the presence of dietary fiber, (6) having γ-oryzanol, and (7) antioxidant activity. Dietary therapy for CKD patients is challenged by the joint needs to provide enough energy and to restrict protein. Patients replaced staple foods with LPFG without side dish restriction. Preliminary study of intervention with 3 months of LPFG reduced constipation probably by increased *Blautia wexlerae*, *Bifidobacteria*, acetic acid, and a decrease in potentially harmful bacteria. Protein intake decreased from 60 to 50 g per day. Urinary protein excretion decreased from 510 to 300 mg per day, and β2-microglobulin from 926 to 250 μg/L. Adherence to the LPFG diet enabled improvement in glomerular and tubular function.

Key Words: chronic kidney disease (CKD), dietary therapy, fermented low protein genmai (LPFG), dysbiosis, leaky gut

TRENDS IN PREVALENCE, MORTALITY AND SOCIAL COST OF CKD

Chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are increasing worldwide, notably among the aged, with diabetes mellitus, chronic glomerulonephritis, and hypertension.[1]

The GDB Chronic Kidney Disease Collaboration estimated CKD prevalence to affect 9.1% of the global population. In 2017, there were 697.5 million cases of CKD, in which stages 1–2 accounted for 5.0%, stage 3 for 3.9%, stage 4 for 0.16%, stage 5 for 0.07%, dialysis for 0·041%, and kidney transplantation for 0.011%.[1] Overall, CKD contributed to cardiovascular disease in 2.6 million deaths and 35·8 million disability-adjusted life-years. In some 27 years, CKD has continued to rise and is among the leading causes of death since aging and hypertension are companion risk factors for CKD.[1]

In Japan, the number of dialysis patients was 334,505, and medical expenses for renal failure 1,534.6 billion yen, which was 3.8% of the national medical expenditure of 40,807 billion yen in 2017.[2] Those aged 65 overspend 2273 billion yen, and the number of deaths due to chronic renal failure is 15,739 per year. The individual QOL and medical expense burden is enormous from hemodialysis.[3] Effective dietary therapy would potentially save much of these medical costs.

EFFECT OF PROTEIN RESTRICTION ON CKD

A low-protein diet reduces uremic symptoms, delays the progression of renal failure, and extends life expectancy.[4] Although numerous trials assess the relationship between protein intake and nephroprotection, randomised clinical trials (RCTs) are not necessarily confirmatory.[4-15] In CKD, adequate energy intake must accompany protein restriction over the long haul otherwise chronic energy deficiency (CED) will supervene. For example, in the RCT conducted by Ihle et al the comparison was 'no restriction' vs. 0.4 g/kg body weight, but protein intake became 0.8 g/kg vs. 0.6 g/kg.[7] The Northern Italian Cooperative Study Group commenced with 1.0 g/kg vs. 0.6 g/kg and this became 0.9 g/kg vs. 0.78 g/kg at the end. Individual eating preferences and usual personal behaviors prevailed, masking the intended intervention.[8,9]

The Modification of Diet in Renal Disease (MDRD)

Corresponding Author: Visiting Prof Shaw Watanabe, Lifescience Research Institute, Tokyo University of Agriculture, 1-1-1, Sakuragaoke, Setagaya, Tokyo 156-8502, Japan.
Tel: +81-70-4097-7505
Email: gwatashaw@gmail.com
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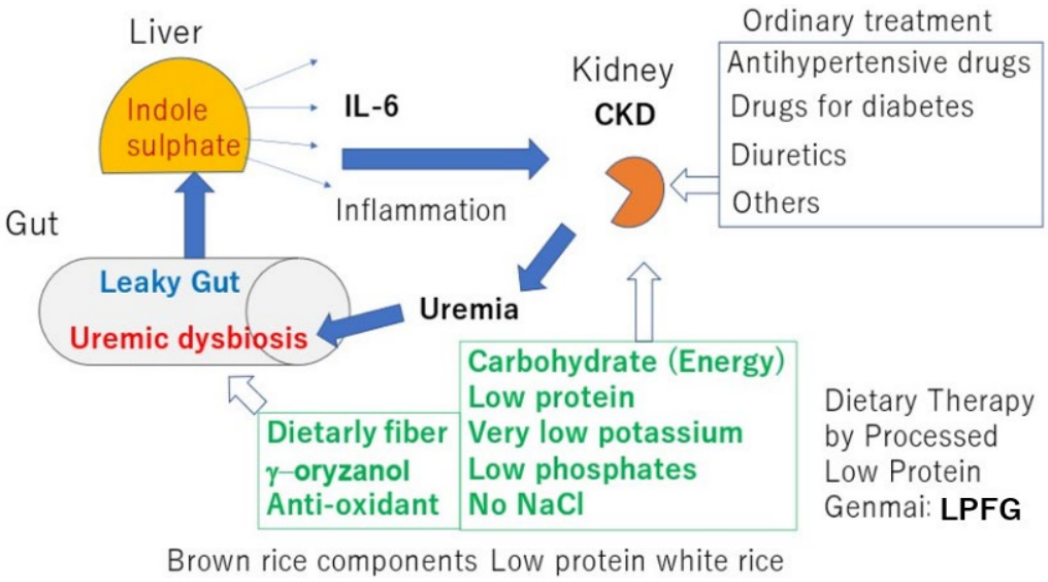

Graphical abstract. Negative spiral of gut-kidney axis in CKD and block by LPFG. In CKD, two pathological conditions, uremic dysbiosis and leaky gut progress CKD and cardiovascular accidents occur. Dysbiosis is associated with endotoxemia and chronic inflammation, disrupting the intestinal barrier and depletion of beneficial bacteria producing short chain fatty acids (SCFAs). Drug therapy cannot stop the increase of end-stage renal disease. To postpone the underlying negative spiral of a gut-kidney axis is essential. The low protein fermented genmai, LPFG, remains the dietary fiber and other functional ingredients which could improve dysbiosis and leaky gut.

study was more instructive.[10] Some 585 patients in group A (GFR 22-55 ml/min/1.73m^2) were divided into two sets; one set was prescribed a normal protein intake (1.3 g/kg/day) and the other a low protein diet (LPD, 0.6 g/kg/day). Actual intakes after two years were 1.11 g/kg and 0.73 g/kg body weight/day, respectively. The 255 patients in Group B (GFR 13-24 ml/min/1.73m^2) were divided into a LPD set (0.6 g/kg/ day) and a very low protein diet (VLPD, 0.28 g/kg/day + 0.28 g/kg amino acid keto acid supplement and multivitamin tablet), although the actual intakes two years later were 0.69 and 0.46 g/kg body weight/day, respectively. Energy intake was set at 30 kcal/kg body weight. The follow-up period was 2.2 years on average, and an additional 9-month revealed a poor prognosis in the VLPD group. As the actual protein intake was found to be above the set level, the low energy intake (22-20 kcal/kg/day) may have contributed to malnutrition and death. We consider that the MDRD study failure to demonstrate the efficacy of LPD was due to an insufficient energy intake.[11] That said, secondary analyses of the MDRD data found a strong relationship between actual protein intake and loss of renal function (p=0.011) or renal death (p=0.001).

We deduce that side dishes, as part of the whole diet, along with long-term eating habits, are crucial determinants of CKD outcomes.[16-19]

THE GUT-KIDNEY AXIS IN CKD PREVENTION AND PROGRESSION

Intestinal microbiota in CKD

A close linkage has been found between the gut and the kidney.[20-22] Chronic kidney disease (CKD) is commonly associated with hypertension and is characterized by immune dysregulation, metabolic disorder, and sympathetic activation, linked to gut dysbiosis, and altered crosstalk between host-microbiota.

In chronic renal failure, the proportion of *Bacteroides sp.* increases, and *Lactobacillus sp.* decreases.[20] Indole, a typical example of a uremic toxin, is raised in the gut. Decreased *Lactobacillus* reduces TLR2 expression on the surface of enteral cells, so loosening and lessening tight junctions, increasing intestinal permeability. This leaky gut situation increases the systemic absorption of indole, which is converted to indoxyl sulfate in the liver and exacerbates systemic inflammation. Increased indoxyl sulfate results in elevated cytokines such as IL-6, with cardiovascular complications. Thus, in CKD, uremic dysbiosis and a leaky gut, progress CKD progression and increase cardiovascular risk.[21-23]

The hallmark of intestinal dysbiosis is a reduction of bacteria mainly producing short-chain fatty acids (SCFA) and, in the case of CKD/ESRD, an increase in proteolytic microbes that accentuate uremic toxicity.

Dysbiosis is associated with endotoxemia and chronic inflammation, with disruption of the intestinal barrier and depletion of beneficial bacteria producing SCFAs. Coexistent T2DM and CKD/ESRD is increasingly found in clinical practice and share similar intestinal microbiotal profiles and function.

Effects of genmai (brown rice) on gut microbiota

We have found that *genmai* (brown rice) consumption has health promoting associations for body weight, BMI, and bowel function.[24-26] The GENKI ("Genmai Evidence of Nutrition for Kenko (health Innovation") study was started in 2016. This epidemiological prospective cohort study sought to clarify how eating *genmai* might enhance caused their health and wellbeing.

Genmai eaters prefer to eat plant-based Japanese foods, avoiding meat and dairy products.[24-26] They dislike oily and spicy tastes, and select foods based on freshness, being 'organic', having no additives, not genetically modi-

fied and domestically produced. Their intestinal microbiota are dominantly *Faecalibacterium prausnitzii* (5.28%) and *Blautia wexlerae* (3.67%).[25] The former is a butyrate producer, and the latter immunomodulating. Dietary fiber and γ-oryzanol in brown rice presumptively normalizes bowel movements.[27]

Intestinal microbiota and short-chain fatty acid status with brown rice consumption

As the *genmai* eater has a characteristic profile of microbiota, we considered whether tried to *genmai* consumption is associated with short-chain fatty acid production. [28]

Thirty healthy participants ate brown rice *genmai* onigiri (rice cakes) 5/week as a business lunch for 12 weeks and assessed intestinal microbiota and short-chain fatty acid status. Pre-and post-questionnaires, daily activity records, monthly blood pressure measurements, and body composition were obtained. Pre- and post-intervention fecal samples allowed intestinal microbiota and short-chain fatty acid profiles to be documented and associated with IL-6, CRP, and TNFα as inflammatory biomarkers.

Bodyweight decreased in about half the participants, and bowel habits improved significantly. Dominant microbiota were *Firmicutes* (around 65%), *Actinobacteria* (15-17%), *Bacteroidetes* (5-7%), and less than 1% of *Proteobacteria*, *Verrucomicrobia*, and *Fusobacteria.* elete *Actinobacteria* increased and *Proteobacteria* decreased. Short-chain fatty acids, acetate and propionate declined, while n-butyrate and i-valerate slightly increased. Acetate and propionate were positively correlated with IL-6, while n-butyrate, and n-valerate were positively correlated with IL6 and CRP. Isobutyrate and isovalerate were negatively correlated with TNFα. The upper tertile of *genmai* eaters demonstrated generally beneficial effects.

LOW PROTEIN FERMENTED GENMAI (LPFG): A MEDICAL RICE FOR CKD

LPFG production

Protein-reduced brown rice has prospects for better CKD management in rice-based food cultures.[29-31] Conventional low protein white rice has not been widely used because of taste, lack of professional advocacy, and poor patient awareness of the merits of a low protein diet in their management.[32] According to the Society of Nephrology in Japan, only 4 to 5 percent of CKD patients receive low protein diet therapy.[33]

Rice grains are covered with an impenetrable wax layer for proteolytic enzymes. Brown rice is also usually contaminated with aerobic spores and other pathogens are present in the grain epidermis. These represent technical obstacles to preparing low-protein brown rice.[34-36]

Low-protein fermented *genmai* (LPFG) has been developed by the Japanese Medical Rice Association in a consortium with the Ministry of Agriculture, Forestry and Fisheries' "Accumulation and Utilization of Knowledge" initiative. The final packed rice is produced from selected raw rice by a series of technologies involving surface treatment by high-pressure steam, protein removal by lactic acid bacteria and enzyme solutions, hygienic rice cooking and packaging.[36]

A two-step fermentation efficiently extracts proteins. After cleaning the surface with a citrate solution, the rice is immersed in a proteolytic enzyme solution with *Lactobacillus Plantarum* under anaerobic conditions. After first and second anaerobic fermentations, the rice is immersed in the same *Lactobacillus*-containing solution for 1.5 days at 40°C. Washing with water removes any surplus. After washing again with cold water, the product is drained. After fermentation, a cleaning process is undertaken, involving the drainage of the secondary fermentation. After that, the rice is washed with running water for two hours. Fermentation products such as organic acids and proteins generated during fermentation are washed away with decomposing substances and residual lactic acid bacteria. After the removal and washing treatment, the protein content is measured with a Dumas Nitrogen Analyzer NDA701,[37] and the rice packed in a plastic tray and steam-cooked.

LPFG composition and functionality

Certification of the manufacturing process as a JAS (Japan Agriculture Standard) is approved. In comparison with low-protein white rice, the LPFG has the following characteristics: (1) the same energy value, (2) a protein content is less than 1/10th, (3) potassium almost zero, (4) phosphorus less than a quarter, with retention of the brown rice phytonutrient profile by way of (5) dietary fiber, (6) γ-oryzanol, and (7) antioxidant ability (Table 1).

Macronutrients and mineral content are shown in Table 1. LPFG has 0.2 g protein /100 g boiled rice.[36] The proportion of dietary fiber remaining was two-thirds that of the original brown rice, and water-soluble fiber was more likely to be removed than insoluble dietary fiber. Remaining protein composition was 37-39 kD gluterin a 13.7%, no 26 kD globulin, 11 kD prolamin at 10.6%, 13 kD prolamin at 36.9%, 76 kD and 39 kD precursors, 11.9% and 18.9% respectively.

Almost no potassium and little phosphate are additional potential benefits in CKD management. Nutritionally relevant genmai factors identified included dietary fiber, and γ-oryzanol. There was residual antioxidant activity. The net nutritional profile has promise for gut health conducive to CKD management.

A pack of PLPG contains 154 g of LPFG (240 kcal; 3 units), with a protein content only 0.2-0.3 g. A patient consuming three packages a day would ingest 720 kcal (9 units) and 0.9 g of protein. One pack contains 2.25 mg of potassium and 76.5 mg of phosphorus, and no detectable NaCl. Dietary fiber content is 4.5 g, and γ-oryzanol is 28.4 mg, with potential to stabilize intestinal microbiomes and ecology. The antioxidant capacity of 300 umol TEQ, is of note, but generally an inadmissible nutritional regulatory claim.[38-39] These LPFG properties in a staple food in rice-based food cultures, are of potential therapeutic value in CKD.

LPFG Usage in CKD management

Patients with CKD often have uremic dysbiosis and intestinal flora changes. Uremic toxins are considered to cause micro-inflammation, with widespread adverse effects on

Table 1. Comparison of nutrients in brown rice, low protein fermented genmai and remained %

Item	Brown rice	LPFG	% remained
Energy (kcal)	244	156	63.9
Water (g)	40.7	62.2	152.8
Carbohydrate (g)	57.1	36.3	63.6
Sugar (g)	55.6	35.3	63.5
Protein (g)	1.3	0.2	15.4
Lipid (g)	1.9	1.3	68.4
Ash (g)	0.1	0.1	100
Potassium (mg)	85.3	0.5	0.6
Phosphate (mg)	115	17	14.8
Dietary fiber (g)	1.5	1	66.7
γ-oryzanol (mg)	10.4	6.3	60.6
NaCleq (g)	0.0041	0.003	73.2
Na (mg)	2.5	1.8	72
K (mg)	85.3	0.5	0.6
Ca (mg)	6	6	100
Mg (mg)	47.5	2.2	4.6
P (mg)	115	17	14.8
Fe (mg)	0.4	<0.1	nd
Zn (mg)	0.76	0.12	15.8
Cu (mg)	0.1	<0.1	nd
Mn (mg)	0.83	0.05	6
As_2O_3 (μg)	0	0	0
Cd (μg)	0	0	0
Vitamin B1 (mg)	0.12	<0.01	nd
Arg (mg)	240	nd	0
Lys (mg)	110	nd	0
His (mg)	77	nd	0
Phe (mg)	140	nd	0
Thr (mg)	120	1	0.9
Leu (mg)	220	nd	0
Ileu (mg)	110	nd	0
Met (mg)	66	nd	0
Val (mg)	160	nd	0
Ala (mg)	160	nd	0
Gly (mg)	140	nd	0
Pro (mg)	130	nd	0
Glu (mg)	470	nd	0
Ser (mg)	140	nd	0
Thr (mg)	100	nd	0
Asp (mg)	260	nd	0
Try (mg)	42	2	4.8
Cys (mg)	58	nd	0
ORAC total (umol/Teq)	350	300	85.7
ORAC Hydrophilic (umol/Teq)	150	100	66.7
ORAC lipophilic (umol/Teq)	200	200	100

Nd: not detected.
†All values are /100 g boiled rice.

organ function. LPFG might mitigate this pathogenesis of CKD.

The Japanese guideline for protein intake is 0.6-0.8 g/kg body weight/day for CKD stage 4 and stage 5.[13] The international consensus is 0. 4-0.6 g/kg body weight, so the Japanese guideline seems less restrictive. We concur with 0.5 g/kg body weight, but Japanese clinicians do not in general agree with the lower guideline. This has motivated our group to design a dietary approach with a LPFG pack as the staple for patients accustomed to rice consumption, with complementary nutritious side dishes. In this way, protein intake could be as low as -10 g/day and participants could maintain an acceptable food intake pattern.

As indicated above, low protein diets for kidney disease may be energy deficient, a challenge in need of expert guidance. We, therefore, have recommend that energy source units, provided in accordance with body weight, namely "bodyweight x 0.4 unit", where one unit is 80 kcal. For example, a 60 kg patient would consume 60 x 0.4=24 units, being eight units per meal. Energy deficiency can thus be avoided. Protein restriction is thereby subconscious and supported by side dish provision as a routine. This can be organized by a dietician or health educator, in accordance with the Japanese dietary guidelines and clinical situation.[40] (Figure 1)

CKD patients practice two dietary methods in the LPFG system: they assess energy intake units in relation to body weight by a factor of 0.4 units, and they know that one unit is 80 kcal. This happens to be the same as in the food exchange table of the Diabetes Society in Japan. The 0.4 unit is 32 kcal and matches the 30-35 kcal guideline. The protein intake from each side dish is about 10 g (about 50 g of meat or fish).

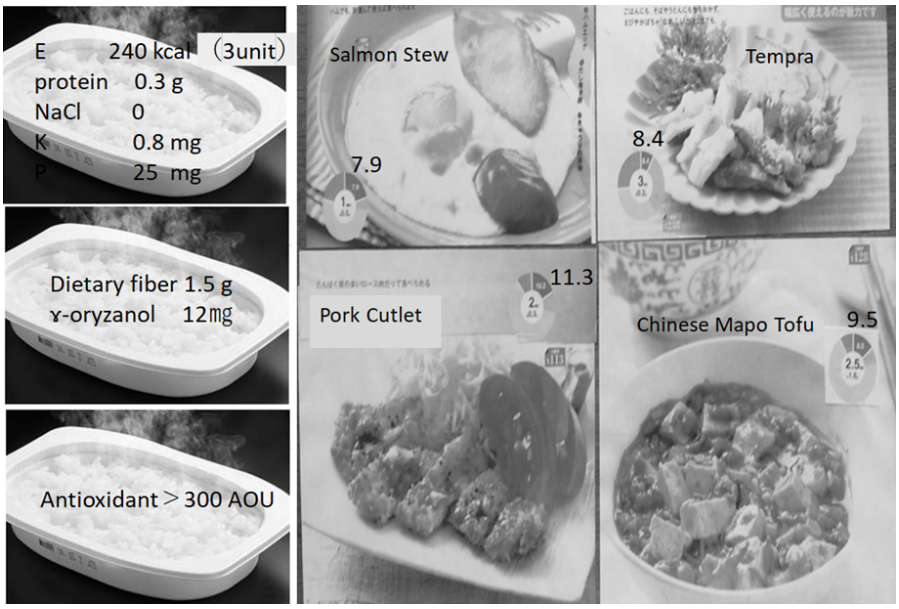

Figure 1. Dietary therapy by using LPFG. Selection of side dishes becomes wide and patients can eat almost anything that they prefer. Numbers in figures are protein content. Food icon shows proportion of protein, lipid, carbohydrate and antioxidant activity as a surrogate marker of green-yellow vegetables. CKD patients should be aware of only two things: (1) energy intake is body weight * 0.4 and 9 unit from rice pack + 10 or more unit from side dishes, (2) around 10 g/dish of protein is allowed in side dishes.

CKD MANAGEMENT EXPERIENCE WITH LPFG AND SIDE DISHES TO IMPROVE THE GUT-KIDNEY AXIS

To evaluate the direct nephro-protective effect of low protein brown rice, we conducted a trial that focused on intestinal health and nephropathy, as well as how intestinal microflora modification might increase in short-chain fatty acid production, a putative risk mitigator. In addition, we were interested in whether the intake of low phosphate of LPFG might be associated with a low FGF23-Klotho gene-product, a phosphate metabolism regulator.[41-42]

Dietary modification is essential in renal insufficiency, but adherence is not easy. However, in rice-based food cultures, substitution for white rice with a LPFG based diet can more liberally include nutritious side dishes and maintain good adherence to protein intake restriction (Figure 1).

In an exploratory study, 30 outpatients with renal failure at Keio Hospital were studied for FPLG acceptability (Adachi K, Makino S, Watanabe S, unpublished) They consumed two LPFG packages per day for three months. Changes in intestinal bacteria and short-chain fatty acids, urinary protein, and renal function were evaluated. At three months, protein intake had decreased from 60 g to 50 g/day, and constipation had remitted. Urinary protein decreased from 510 mg to 300 mg/ day, and β2-microglobulin reduced from 926 to 250 μg/L. eGFR plateaued from 35 to 33 ml/min/1.73M^2. The LPFG diet did not apparently contribute adversely to glomerular or tubular function. A likely effect of the brown rice was evident by a predominance of *Blautia wexlerae* and increased *Bifidobacteria*, acetic acid, and a decrease in potentially harmful bacteria. The protein intake varied from 0.4 to 1.5 g/kg body weight. One quarter of patients increased protein intake, all of them obese men. With a little protein from side dishes, it appeared easier to reduce protein intake to 0.5 g/kg body weight.

CONCLUSIONS

Diet therapy increases the prospect of effective management of CKD with greater program adherence. LFPG can address the clinical needs of the increasingly numerous sufferers from renal failure and its sequelae. Inevitably, there is concern that a low protein diet will contribute to frailty and sarcopenia but, in the face of protein energy malnutrition, energy deficiency and associated poor dietary quality may be the more important target.[43-45] In fact, less overall dietary restriction and achievable satiety are possible with LPFG.[46,47] More investigation to characterize the intestinal microbiota in CKD, especially in diabetic nephropathy, should allow the LPFG diet to be positioned appropriately.

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AUTHOR DISCLOSURES

The authors have no commercial conflict of interest. KA and SW have clinical responsibility for this study.TH and JM performed the microbiomic and short-chain fatty acid investigations.

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