

Diabetes & its Complications

The International Conference on Dietary Therapy for Chronic Kidney Disease with Special Reference to the Gut-Kidney Linkage and Low Protein Brown Rice (*Genmai*)

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The number of individuals with all-stage chronic kidney disease (CKD) reached almost 700 million in 2017, 9.1% of the world's population, primarily due to the increase in diabetes and hypertension [1]. CKD diagnoses resulted in 1.2 million deaths in 2017. Despite the increases in hemodialysis and kidney transplantation, the availability of this renal therapy is still limited in many world regions with a high burden of CKD. Recently, the negative spiral of the gut-renal linkage has been found behind CKD [2-4]. Uremic dysbiosis causes endotoxemia and chronic inflammation, the destruction of the intestinal barrier, and the depletion of beneficial bacteria producing short-chain fatty acids.

Under such conditions, the Medical Rice Association organized the International Workshop on Dietary Therapy for Chronic Kidney Disease (CKD) on March 4-5, 2023, in Tokyo. The workshop was backed by the Japan Kidney Association and the Japanese Society of Anti-aging Medicine and sponsored by the Ministry of Agriculture, Forestry and Fisheries (MAFF) via the PRISM fund. The Webinar and the on-demand report were available.

The conference focused on the gut-kidney linkage and low protein *genmai* (brown rice), which received approval from the Ministry of Agriculture, Forestry, and Fisheries meeting the Japanese Agricultural Standard's JAS 0027 product and process certification criteria [5].

At the opening session, Professor Naoki Kashihara, Chairman of the Ministry of Health, Labour and Welfare Committee, talked about eight years of experience in renal disease control at the national level [6]. In July 2018, the Renal Disease Countermeasures Investigative Committee Report, which to further promote kidney disease countermeasures, was widely distributed to local

governments and organizations nationwide. However, preventing end-stage renal disease (ESRD) failed by drug therapy alone because it could not suppress the number of ESRD patients.

Mr. Toyohisa Aoyama, Director General of the Rural Development Bureau, MAFF, stressed the importance of food-based dietary therapy. CKD is one of the best examples of conditions that can be treated by dietary intervention. In Japan, the number of kidney dialysis patients exceeds 340,000, and the overall medical cost for these patients is approximately 15 billion US dollars annually [7]. Given these circumstances, it is essential to focus on maintaining our fitness, returning from a pre-disease state, and slowing down the progression of CKD. In Japan, there is a saying called "*Ishoku Dogen*." According to this concept, medicine and foods are derived from the same sources; they work on the body to keep it healthy [8]. The "low-protein processed brown rice package" (JAS0027) can address two significant social challenges: reducing medical expenses and revitalizing paddy field agriculture by fair trade. He expected our packed low protein *genmai* to be recognized internationally to help curb the increase of dialysis patients worldwide.

Professor Duo Li, Quindao University and President emeritus, Asia Pacific Clinical Nutrition Society, talked about the severe problem of CKD as a silent killer in China. The low-protein diet was a traditional treatment to decrease proteinuria until the 1960s when hemodialysis became available [9]. Since the 1980s, the development of diuretics, antihypertensive, antidiabetic, and recent SGL-2 inhibitors has replaced the protein-restricted diet as the primary treatment. However, despite these drug therapies, the number of ESRD patients has not decreased [6]. Professor Csaba Kovesdy, University of Tennessee, USA, stressed the

importance of controlling protein energy malnutrition and introduced several new renoprotective medication classes [10]. Professor Angela Yee-Moon Wang discussed dietary interventions currently recommended for CKD patients worldwide and spoke about her clinical experience [11]. Professor Raymond Vanholder summarized his life-long study on uremic toxicity [12]. He found tryptophan metabolism yielded notorious toxins like indoxyl sulfate, but an alternate pathway produced indole-propionic acid, and indole-carbohydrate, regulators of insulin sensibility and neuroprotectors [13]. Unfortunately, the removal of uremic toxins by hemodialysis has not been successful in addressing these issues.

For this solution, Dr. Shaw Watanabe introduced the effect of newly developed low protein *genmai* by deleting the rice protein from the whole brown rice by a particular combination of enzyme solution and *Lactobacillus plantaris* [5]. It saves carbohydrates (energy source), but protein, potassium, phosphate, and NaCl were removed to a very low level. At the same time, the presence of dietary fiber, γ -oryzanol, and antioxidant activity remained 60% of the original *genmai*.

Dietary therapy for CKD patients is complex because of the simultaneous control of energy source intake and protein restriction. A preliminary study of 3 months of a low protein *genmai* diet improved constipation rapidly and decreased γ -proteobacteria like *Escherichia coli* by increasing *Blautia wexlerae* and *Bifidobacteria*. Patients only replaced their staple food with the packed low protein *genmai*. As expected, the protein intake decreased from 60 g to 50 g daily. So, people can easily practice a low-protein diet to reduce protein intake. Production of uremic toxins was significantly decreased, and urinary protein and biomarkers of renal damage were also reduced [4]. The low protein *genmai* could improve the negative spiral of the gut-kidney linkage caused by uremic dysbiosis and leaky gut.

The importance of intestinal microbiota for Japanese longevity was reported by Professor Yuji Naito, Kyoto Prefectural University of Medicine, and Professor Junichiro Irie, Keio University, who reported some trials of bacterial transfer. The importance of lifestyle was reported by two cohorts in Okinawa and Shanghai by Dr. Kunitoshi Iseki and Professor Qi Guo at Shanghai University, who focused on physical fitness.

After the keynote and plenary lectures mentioned above, a panel session was chaired by Shaw Watanabe, Angela Wang, and Junichiro Irie to discuss the following problems of dietary therapy in Japan.

1. Why is diet therapy not popular in CKD treatment in Japan?
2. Is there a nutritional disorder due to low-protein therapy?
3. Is protein restriction therapy valued overseas? How about plant-based foods?
4. Significance of gut-renal linkage in renal failure diet.
5. Difficulties of the renal failure diet.
6. About the future of low-protein rice and brown rice.
7. Is protein restriction therapy valued overseas?

Dr. Lekh Juneja, CEO of Kameda Seika Co. Ltd., presented the

future direction of dietary therapy for CKD. He pointed out that hemodialysis and peritoneal dialysis are the most current treatment for the advanced stage of CKD, but such treatments come with an enormous economic burden. Dietary therapy has been a long-used strategy for managing CKD. In a food culture where rice is the staple food and one of the primary protein sources, incorporating low-protein rice into the daily diet is an efficient strategy for reducing protein and maintaining the taste and overall satisfaction of meals.

The main reason for ignorance of dietary therapy is the inconsistent and contradictory results of Randomized Clinical Trials (RCTs), making it difficult to conduct meta-analyses and develop reliable guidelines [14]. The scheduled protein intake was often excessive at the end of the study, or the difference between the intervention group and the control group became small. Alternatively, total energy intake often becomes insufficient to cause malnutrition by reducing the dose of a meal.

Individual independence is more significant when considering the gut-kidney linkage and other intrabody metabolic relationships. Taste preferences and responses to dietary advice are also influenced by personality [15]. Raymond Vanholder proposed patient-reported outcome measures as a helpful point for evaluation. We would better start the LPFG (Low protein fermented *genmai*) intervention study on CKD patients by the pro- and post-comparison. Restricting protein intake is essential for patients with renal insufficiency, but compliance is complex. A meal that only substitutes white rice by the LPFG package without strict limitations on side dishes is easy to maintain good adherence to protein and mineral controls. Comparing pre- and post-assessment is a straightforward and practical method under the solution-oriented strategy.

Pharmaceutical companies make tremendous investments to have doctors use drugs, while funds from food companies would be one hundredth or less [16]. So, dietary therapy is not initiated by most doctors. The patient's self-reliant will is the key to successful diet therapy and is suitable for collaborative efforts involving health care providers and patients. CKD's silent nature, with its unpredictable symptoms, is a significant barrier to motivating patients' behavioral changes and therapeutic decision-making by healthcare providers. Medical rice for CKD, such as LPFG, has attracted attention because it shows effectiveness for both low-protein diets and improved gut-kidney linkage. Lowered cytokines like IL-6 may ease low-grade inflammation, a risk factor for cardiovascular complications. At the end of the workshop, we adopted the Tokyo declaration as follows.

Tokyo Declaration of Dietary Therapy for Chronic Kidney Disease

In the clinical practice of chronic kidney disease in Japan, the importance of diet therapy has received little attention compared to drug therapy and hemodialysis, and the investment in medical resources is negligible. Compared to the interest in diet therapy overseas, awareness still needs to be improved, and preventive

medicine is necessary. It is challenging to devise side dishes for low protein therapy as part of diet therapy. In addition, there needs to be more interest in dietary therapy considering the gut-kidney linkage. Low-protein brown rice has the potential to be one of the keys to overcoming the above problems. We reached a consensus through the International Workshop on Dietary Therapy for Chronic Kidney Disease (CKD) supported by the PRISM in the Ministry of Agriculture, Forestry, and Fisheries.

A: Pathophysiology of CKD and ESRD

1. Excessive protein intake burdens the kidneys, and a protein-rich diet and uremic state lead to dysbiosis in the intestinal flora.
2. Uremic toxins produced in the intestinal tract leak (the leaky gut), reach the liver and are metabolized into highly toxic uremic poisons.
3. Inflammatory stimulation by toxins causes the liver to release cytokines such as IL6 and CRP, causing mild inflammation throughout the body and causing cardiotoxicity.
4. As this gut-liver-kidney toxicity increases, it forms a negative spiral of the gut-kidney linkage.
5. Unless this negative spiral is improved, we cannot control CKD with antidiabetic drugs, hypertensive drugs, diuretics, etc., that target the kidney.

B: Low protein genmai, JAS0027

1. Low protein *genmai* (brown rice) package is the only food that improves intestinal dysbiosis and leaky gut and is also effective for the kidneys.
2. The energy content in low-protein *genmai* is almost the same as brown rice and white rice. It features brown rice components such as dietary fiber, γ -oryzanol, antioxidant activity, and characteristic low protein, low potassium, low phosphate, and no NaCl. The JAS guarantees internationally credible functional ingredients (JAS0027).

C: Clinical practice

1. Patients can reduce protein intake by 10g by replacing three staple meals with this low-protein *genmai* pack. If the amount of protein in the side dishes is around 10g per meal (50 g of meat or fish), it will make a low-protein meal of about 0.5g/kg body weight without imposing a stressful burden to the patient. Plant protein is more recommended than meat.
2. Dietary therapy requires voluntary efforts by patients, but integrated support by society is also necessary.

D: Public Health and Epidemiology

1. Randomized Clinical Trials to obtain evidence of diet therapy tend to fail, particularly when patients increase protein or have deficient energy intake during the trials. It is difficult to control individual subjects and their diets over time.
2. Voluntary low-protein diets, which are less burdensome, improve patients' QOL and help reduce medical expenses.

3. Evaluating historical evidence and developing new epidemiological methods like pro- and post-comparison is necessary to build evidence of dietary therapy.

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