A nationwide questionnaire study evaluated kidney injury associated with Beni-koji tablets in Japan

Maki Shinzawa[1,2,6], Isao Matsui[1,6], Yohei Doi[1,3,6], Ayumi Matsumoto[1], Atsushi Takahashi[1], Masaomi Nangaku[4] and Yoshitaka Isaka[1]; and Collaborators[5]

OPEN

[1]Department of Nephrology, Graduate School of Medicine, Osaka University, Suita, Japan; [2]Health and Counseling Center, Osaka University, Toyonaka, Japan; [3]Department of Cardiology, Pulmonology, Hypertension and Nephrology, Ehime University Graduate School of Medicine, Ehime, Japan; and [4]Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan

Red yeast rice, traditionally used in Asian cuisine and increasingly marketed as a dietary supplement for cholesterol management, has recently been linked to kidney dysfunction in Japan. In late 2023 to early 2024, multiple cases involving specific Beni-koji (red yeast rice) tablets from three different Beni-koji preparations, prompted a safety reevaluation. Although citrinin, a known nephrotoxin of red yeast rice, was not produced by the implicated strains, new safety concerns emerged. Here, we aimed to investigate the clinical, laboratory, and pathological features of affected patients with a two-phase nationwide survey of Japanese nephrologists. The initial survey captured clinical presentations, while the follow-up survey tracked changes in kidney function and gathered pathological data. Statistical analyses included trend assessments across estimated glomerular filtration rate (eGFR) categories and mixed-effects models for eGFR trajectories. Of 192 patients, 94.1% presented with low eGFR (under 60 ml/min/1.73m^2). Laboratory findings revealed characteristics of Fanconi syndrome, including hypokalemia, hypophosphatemia, hypouricemia, glycosuria, and metabolic acidosis. Creatine kinase levels were not elevated suggesting no rhabdomyolysis related kidney injury. Kidney biopsies showed predominant tubulointerstitial changes, with 50% exhibiting tubulointerstitial nephritis and 32% showing tubular necrosis. Glomerular changes were less prominent. Following product discontinuation and treatment, Fanconi syndrome-related parameters improved significantly. However, 87% of patients still had eGFR under 60 ml/min/1.73m^2 at the last observation. Our findings underscore the need for long-term follow-up of affected individuals and highlight the importance of rigorous safety evaluations for dietary supplements. Further research is necessary to establish definitive causal relationships and long-term outcomes.

Kidney International (2025) **107,** 530–540; https://doi.org/10.1016/j.kint.2024.11.027

KEYWORDS: Beni-koji (red yeast rice); Fanconi syndrome; kidney injury

Lay Summary

In late 2023 to early 2024, multiple cases of kidney dysfunction were reported among users of specific Beni-koji (red yeast rice) tablets in Japan, prompting a safety review. Despite the known risk of citrinin-related nephrotoxicity from red yeast rice, these cases occurred in users of products containing strains reportedly unable to produce citrinin, raising new safety concerns. This study aimed to investigate the clinical characteristics, laboratory findings, and pathologic features of patients who developed kidney dysfunction following the use of Beni-koji tablets through a nationwide questionnaire survey. Most of the 192 patients exhibited Fanconi syndrome with decreased estimated glomerular filtration rate (eGFR; <60 ml/min per 1.73 m^2). Although the electrolyte abnormalities improved after discontinuing Beni-koji tablets, 87.0% of the patients had low eGFR at the last observation. This temporal association between supplement use and kidney dysfunction raises important concerns about supplement safety and highlights the need for careful evaluation of health supplements.

Dietary supplements and functional foods are globally used with the intention of maintaining or improving health. However, these products can sometimes cause adverse effects, including kidney dysfunction.[1–5]

Red yeast rice has a long history of use as an ingredient in various traditional dishes in Japan. For example, it is used in Okinawan cuisine to make “tofuyo,” a type of fermented tofu. This long-standing culinary tradition has contributed to a positive perception of its safety for food use. In recent years, concentrated forms of red yeast rice have been marketed as functional foods primarily for cholesterol management. These

Correspondence: *Yoshitaka Isaka, Department of Nephrology, Graduate School of Medicine, Osaka University, D-11, 2-2 Yamadaoka, Suita, Osaka, 565-0871 Japan. E-mail: isaka@kid.med.osaka-u.ac.jp*

[5]A complete list of the Collaborators is provided in the Appendix.

[6]MS, IM, and YD contributed equally to this work.

Received 30 August 2024; revised 18 November 2024; accepted 22 November 2024; published online 19 December 2024

products, known as Beni-koji tablets (where "Beni" means red, and "Koji" refers to the cultured yeast), fall under the category of "Foods With Function Claims," a regulated category in Japan allowing specific health claims under government-set safety and efficacy standards.[6–8] Beni-koji tablets contain monacolin K, a compound structurally identical to lovastatin.[9–12] This compound is considered to be the primary active ingredient responsible for the cholesterol-lowering effects of these products.

The safety of red yeast rice has been debated internationally, with Europe restricting its use because of potential production of citrinin, a nephrotoxic mycotoxin.[10,13,14] Citrinin primarily targets proximal tubules, causing oxidative stress and mitochondrial dysfunction, which can lead to impaired kidney function.[15] Despite these concerns, Japan's long history of using red yeast rice as a food ingredient initially led to a perception of safety for its use in supplemental form.[11] However, recent events have challenged this assumption.

From late 2023 to early 2024, a significant health concern emerged in Japan when multiple cases of kidney dysfunction were associated specifically with Beni-koji tablets, leading to a voluntary recall by Kobayashi Pharmaceutical Co, Ltd, on March 22, 2024.[16] The recalled products included 3 specific brand names: Beni-koji Choleste-Help, Naishi-Help Plus Cholesterol, and Natto-Kinase SaraSara Granules GOLD, all of which were marketed as cholesterol-lowering Beni-koji containing tablets. This incident was particularly alarming because Kobayashi Pharmaceutical had addressed the known citrinin concern by using a strain reportedly incapable of producing citrinin.[9]

This incident highlights the complex nature of functional foods and dietary supplements and their potential for unforeseen safety issues, even when known risks are addressed. Given these concerns, the present study aimed to comprehensively investigate the clinical characteristics, laboratory findings, and pathologic features of patients affected by Beni-koji tablets in Japan. Furthermore, we assessed the severity and potential reversibility of the associated kidney dysfunction, providing crucial insights for both clinical management and regulatory considerations specific to these functional food products.

METHODS

Study design and participants

We conducted a 2-phase nationwide questionnaire survey to investigate kidney dysfunction or urinary abnormalities potentially associated with Beni-koji tablets.

Phase 1: initial survey. Using Google Forms, we developed a comprehensive questionnaire to capture the initial presentation and clinical characteristics of the affected patients. The questionnaire was distributed to all physicians who are members of the Japanese Society of Nephrology on March 27, 2024. The survey remained open for responses until April 30, 2024.

Phase 2: follow-up survey. To gain a more detailed understanding of the clinical course and pathologic findings, we conducted an additional follow-up survey. On May 13, 2024, this supplementary questionnaire was sent to the physicians who responded to the initial survey. We accepted responses until June 3, 2024. The follow-up questionnaire focused on the following: (i) updated laboratory data to track the progression or resolution of kidney dysfunction; and (ii) detailed information about light and/or electron microscopic findings from kidney biopsies, where available.

Questionnaire

The questionnaire items for phases 1 and 2 are summarized in Supplementary Tables S1 and S2, respectively. This study was approved by the Ethics Committee of Osaka University Hospital (approval number 24010). The study protocol adhered to the ethical guidelines for medical and health research involving human subjects established by the Japanese government. In accordance with these guidelines and owing to the observational nature of the study, we used an opt-out approach.

Histologic analysis

To illustrate the characteristic histopathologic findings, we have presented a representative image from a kidney biopsy case showing hematoxylin and eosin, periodic acid–Schiff, periodic acid–methenamine silver, and elastica Masson staining. The biopsy specimen was digitized using a NanoZoomer, a whole-slide imaging scanner (Hamamatsu Photonics).

Immunofluorescence staining was performed on paraffin-embedded kidney biopsy specimens using standard protocols. Briefly, antigen retrieval was conducted using citrate buffer at 120 °C for 20 minutes, followed by blocking with 1.5% bovine serum albumin/Tris-buffered saline. Primary and secondary antibodies were both used at 1:200 dilution. A detailed list of antibodies used is provided in Supplementary Table S3. As a control, we used paraffin-embedded kidney biopsy specimens from a patient with IgA nephropathy (estimated glomerular filtration rate [eGFR] 102 ml/min per 1.73 m^2 and urinary protein 0.46 g/g creatinine). Images were captured using an FV3000 confocal microscope (Evident). Written informed consent was obtained from the patients for the use of the biopsy images in our study.

Statistical analysis

Continuous variables are summarized as medians with interquartile ranges, whereas categorical variables are presented as frequencies and proportions. Patient characteristics were evaluated according to tertiles of eGFR levels at the initial visit. *P* values for trends across kidney function categories were assessed using the Jonckheere-Terpstra test for continuous variables and the Cochran-Armitage test or the linear-by-linear association test for categorical variables. The eGFR trajectories were analyzed using mixed-effects models for repeated measures.[17] This model incorporated the fixed effects of age, sex (defined based on biological characteristics [male/female] as recorded in medical records), and time

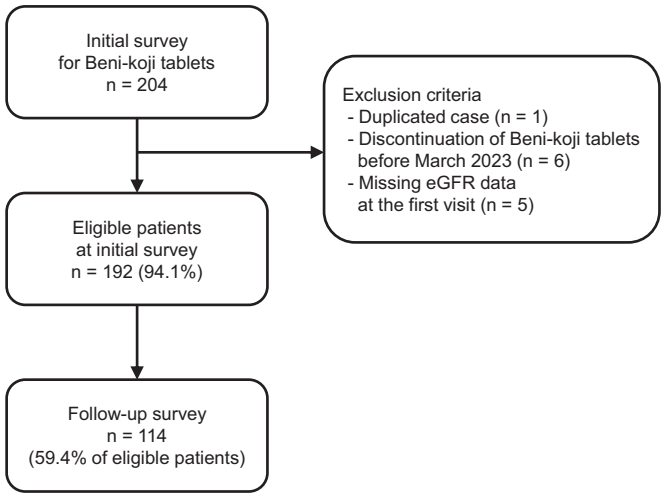

Figure 1 | Flow diagram of patient selection and survey processes. The patient selection process and survey flow for the study of Beni-Koji tablet–associated kidney dysfunction are illustrated. The initial survey included 204 patients with suspected Beni-koji tablet–related adverse events. After applying the exclusion criteria, 192 eligible patients (94.1% of initial cases) were included in the primary analysis. A follow-up survey was conducted with 114 patients, representing 59.4% of the eligible patients in the initial survey. This 2-phase approach allowed for comprehensive data collection and assessment of clinical outcomes over time. eGFR, estimated glomerular filtration rate.

(linear, quadratic, and cubic) while treating individual patients as random effects to account for interpatient variability. To investigate the potential impact of kidney injury severity on eGFR trajectories, the interaction terms between kidney injury categories at the initial visit and time (linear, quadratic, and cubic) were incorporated into the model. In addition, to evaluate the treatment effects of corticosteroid therapy, the fixed effects of corticosteroid use, eGFR at the initial visit, interaction terms of corticosteroid use by time (linear, quadratic, and cubic), and eGFR at the initial visit by time (linear) were incorporated into the model. To further investigate the origin of proteinuria, we calculated the Pearson correlation coefficient for the associations of natural logarithm of urinary protein-to-creatinine ratio and natural logarithm of urinary β2-microglobulin with serum levels of potassium, phosphorus, and uric acid, respectively. All statistical tests were 2 tailed, with statistical significance set at $P < 0.05$, and all analyses were performed using STATA version 18.5 (Stata Corp).

Conventional units of laboratory data can be converted to Système International (SI) units as follows: BUN (mg/dl × 0.357 = mmol/l); uric acid (mg/dl × 0.0595 = mmol/l); creatinine (mg/dl × 76.25 = μmol/l); calcium (mg/dl × 0.25 = mmol/l); adjusted calcium (mg/dl × 0.25 = mmol/l); phosphorus (mg/dl × 0.323 = mmol/l); creatine kinase (units per liter [IU/l] × 0.0167 = μkat/l); albumin (g/dl × 10 = g/l); and C-reactive protein (mg/dl × 10 = mg/l).

RESULTS

Patient selection and study design

In this study, the selection and analysis of patients followed a comprehensive 2-phase process, as illustrated in Figure 1. The initial survey identified 204 suspected cases of Beni-koji tablet–associated kidney dysfunction. We excluded 1 case for duplication, 6 cases for discontinuation of Beni-koji tablets before March 2023, and 5 cases for missing eGFR data at the initial visit. The exclusion of cases before March 2023 was based on the identification of specific manufacturing lots associated with reported adverse reactions that were manufactured after March 2023.[16] After applying the exclusion criteria, 192 (94.1%) eligible patients were included in the primary analysis. The follow-up survey received responses from 59.4% of the eligible patients (114 of 192).

Patient demographics and Beni-koji tablet use patterns

The study cohort (n = 192) comprised 62 males (32.3%), with a predominance of patients aged 50 to 69 years (71.9%; Table 1). Most patients (174 [97.2%]) had been using Beni-koji Choleste-Help exclusively. Medical history data showed that 10.0% of the patients had kidney disease, 20.5% had hypertension, and 5.3% had diabetes (Table 1).

Approximately 40% of the patients started taking Beni-koji tablets before March 2023, and 51.3% had used the drug for >8 months (Supplementary Table S4). Tablet discontinuation gradually increased from November 2023, peaking in March 2024, following the voluntary recall announcement. No discernible trend was observed between initial eGFR categories and the duration of tablet use (Supplementary Table S4).

Most patients sought medical attention between December 2023 and March 2024, peaking in March 2024 (36.6%; Supplementary Table S5). The most common chief complaints at the initial visit were kidney dysfunction (56.8%), loss of appetite (50.0%), and general fatigue (49.0%). Notably, the prevalence of appetite loss and general fatigue significantly increased as eGFR declined across the tertiles (Supplementary Table S5).

Table 1 | Patient characteristics, laboratory data, and treatment, stratified by eGFR levels at initial visit

Parameters (n: all, low/medium/high eGFR tertile)	All	Tertile of eGFR at the initial visit			P_{trend}
		Low	Medium	High	
Male sex (192, 64/65/63)[a]	62 (32.3)	19 (29.7)	19 (29.2)	24 (38.1)	0.312
Age, yr (192, 64/65/63)[a]					0.002
30–39	5 (2.6)	0 (0.0)	0 (0.0)	5 (7.9)	
40–49	27 (14.1)	9 (14.1)	7 (10.8)	11 (17.5)	
50–59	74 (38.5)	18 (28.1)	31 (47.7)	25 (39.7)	
60–69	64 (33.3)	24 (37.5)	21 (32.3)	19 (30.2)	
≥70	22 (11.5)	13 (20.3)	6 (9.2)	3 (4.8)	
History					
Kidney disease (110, 43/35/32)[a,b]					0.057
Yes	11 (10.0)	7 (16.3)	3 (8.6)	1 (3.1)	
No/unknown	99 (90.0)	36 (83.7)	32 (91.4)	31 (96.9)	
Hypertension (112, 46/34/32)[a,b]					0.567
Yes	23 (20.5)	10 (21.7)	8 (23.5)	5 (15.6)	
No	89 (79.5)	36 (78.3)	26 (76.5)	27 (84.4)	
Diabetes (113, 46/35/32)[b]					0.521
Yes	6 (5.3)	3 (6.5)	2 (5.7)	1 (3.1)	
No	107 (94.7)	43 (93.5)	33 (94.3)	31 (96.9)	
Brand names of Beni-koji tablets (179, 59/59/61)[a]					0.103
Only Beni-koji Choleste-Help	174 (97.2)	58 (98.3)	59 (100.0)	57 (93.4)	
Others[c]	5 (2.8)	1 (1.7)	0 (0.0)	4 (6.6)	
Laboratory data					
Blood test					
WBC count, $\times 10^3/\mu l$ (190, 64/65/61)[d]	6.8 (5.4–8.4)	8.3 (7.4–10.2)	6.3 (5.4–8.2)	5.5 (4.5–6.7)	<0.001
Eosinophil, % (177, 62/61/54)[d]	1.6 (0.4–2.8)	1.0 (0.1–2.0)	1.6 (0.4–2.6)	2.2 (1.1–3.2)	<0.001
Sodium, mEq/l (191, 64/64/63)[d]	140 (138–142)	138 (136–141)	141 (139–142)	140 (139–142)	<0.001
Potassium, mEq/l (192, 64/65/63)[d]	3.5 (3.0–3.9)	3.2 (2.9–3.7)	3.4 (3.0–3.7)	3.7 (3.3–4.1)	<0.001
BUN, mg/dl (191, 64/65/62)[d]	18.0 (13.9–24.0)	28.9 (21.6–54.0)	17.8 (15.3–19.7)	14.1 (11.0–16.3)	<0.001
Uric acid, mg/dl (189, 64/63/62)[d]	1.8 (1.4–2.9)	2.1 (1.7–3.1)	1.6 (1.2–1.9)	1.9 (1.4–4.3)	0.274
Creatinine, mg/dl (192, 64/65/63)[d]	1.6 (1.2–2.5)	3.1 (2.5–4.0)	1.5 (1.3–1.8)	1.0 (0.9–1.2)	<0.001
eGFR, ml/min per 1.73 m^2 (192, 64/65/63)[d]	30.0 (17.2–42.4)	15.2 (10.2–17.2)	30.0 (27.7–32.2)	48.0 (42.4–53.4)	<0.001
Calcium, mg/dl (180, 63/62/55)[d]	9.1 (8.7–9.5)	9.1 (8.8–9.5)	9.0 (8.7–9.2)	9.1 (8.6–9.5)	0.587
Adjusted calcium, mg/dl (180, 63/62/55)[d]	9.1 (8.8–9.6)	9.3 (8.9–9.6)	9.1 (8.8–9.4)	9.1 (8.6–9.6)	0.220
Phosphorus, mg/dl (170, 60/58/52)[d]	2.1 (1.6–2.9)	2.4 (1.9–3.5)	1.8 (1.5–2.2)	2.2 (1.4–3.2)	0.003
CK, IU/l (168, 57/59/52)[d]	114 (78–157)	129 (75–210)	107 (71–151)	115 (84–145)	0.318
Albumin, g/dl (188, 63/64/61)[d]	4.2 (3.9–4.5)	4.2 (3.8–4.6)	4.1 (3.9–4.3)	4.3 (4.1–4.5)	0.268
CRP, mg/dl (180, 63/62/55)[d]	0.1 (0.0–0.2)	0.1 (0.0–0.5)	0.1 (0.0–0.1)	0.0 (0.0–0.1)	<0.001
Bicarbonate ion, mmol/l (137, 52/48/37)[d]	18.2 (15.5–22.3)	14.9 (12.4–17.4)	19.3 (16.6–20.9)	24.3 (20.3–26.3)	<0.001
Urinalysis					
Urinary protein (190, 64/64/62)[a]					
Negative or trace	31 (16.3)	1 (1.6)	5 (7.8)	25 (40.3)	<0.001
1+	35 (18.4)	7 (10.9)	9 (14.1)	19 (30.6)	
2+	92 (48.4)	40 (62.5)	37 (57.8)	15 (24.2)	
3+	32 (16.8)	16 (25.0)	13 (20.3)	3 (4.8)	
Urinary glucose (190, 63/65/62)[a]					<0.001
Negative or trace	39 (20.5)	2 (3.2)	8 (12.3)	29 (46.8)	
1+	18 (9.5)	1 (1.6)	7 (10.8)	10 (16.1)	
2+	16 (8.4)	6 (9.5)	9 (13.8)	1 (1.6)	
3+	117 (61.6)	54 (85.7)	41 (63.1)	22 (35.5)	
Occult blood (188, 63/65/60)[a]					<0.001
Negative or trace	33 (17.6)	9 (14.3)	11 (16.9)	13 (21.7)	
1+	81 (43.1)	33 (52.4)	37 (56.9)	11 (18.3)	
2+	23 (12.2)	18 (28.6)	4 (6.2)	1 (1.7)	
3+	51 (27.1)	3 (4.8)	13 (20.0)	35 (58.3)	

(*Continued on following page*)

Table 1 | (Continued) **Patient characteristics, laboratory data, and treatment, stratified by eGFR levels at initial visit**

Parameters (n: all, low/medium/high eGFR tertile)	All	Tertile of eGFR at the initial visit			P_{trend}
		Low	Medium	High	
UPCR, g/gCre (177, 60/61/56)[d]	1.6 (0.8–2.6)	2.3 (1.7–3.1)	1.9 (1.1–2.9)	0.6 (0.2–1.4)	<0.001
Urinary β2MG, $\times 10^3$ μg/l (160, 51/53/56)[d]	16.9 (1.3–33.1)	18.2 (2.2–33.6)	24.3 (11.8–43.9)	3.5 (0.1–25.4)	0.011
Urinary NAG, U/l (151, 50/53/48)[d]	22.6 (12.4–31.4)	23.3 (14.5–31.5)	25.9 (14.4–31.9)	15.6 (6.5–28.6)	0.018
Treatment					
Use of corticosteroids (192, 64/65/63)[a]	34 (17.7)	17 (26.6)	10 (15.4)	7 (11.1)	0.022
Dialysis (192, 64/65/63)[a]	6 (3.1)	6 (9.4)	0 (0.0)	0 (0.0)	0.002

BUN, blood urea nitrogen; CK, creatine kinase; Cre, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; β2MG, β2-microglobulin; IQR, interquartile range; IU/L, units per liter; NAG, N-acetyl-β-D-glucosaminidase; SI, Système International; UPCR, urinary protein-to-creatinine ratio; WBC, white blood cell.
[a]Categorical variables are presented as n (%).
[b]Medical history data (kidney disease, hypertension, and diabetes) were obtained in the follow-up survey, whereas all other data were collected in the initial survey.
[c]Others in the brand names of Beni-koji tablets category include patients using Naishi-Help Plus Cholesterol or Natto-Kinase SaraSara granules GOLD alone, or in combination with Beni-koji Choleste-Help.
[d]Continuous variables are presented as median (IQR).
Conventional units of laboratory data can be converted to SI units as follows: BUN (mg/dl × 0.357 = mmol/l); uric acid (mg/dl × 0.0595 = mmol/l); Cre (mg/dl × 76.25 = μmol/l); calcium (mg/dl × 0.25 = mmol/l); adjusted calcium (mg/dl × 0.25 = mmol/l); phosphorus (mg/dl × 0.323 = mmol/l); CK (IU/l × 0.0167 = μkat/l); albumin (g/dl × 10 = g/l); and CRP (mg/dl × 10 = mg/l). This table presents patient characteristics, laboratory data, and treatment information. The "All" column shows data for the entire study population, whereas the subsequent columns display data for each eGFR tertile (low, medium, and high) at the initial visit, allowing for comparison across different levels of kidney function at presentation. The numbers in parentheses in the "Parameter" column represent the data counts for each item (from left to right: total data count, data counts for low/medium/high eGFR tertiles). Please note that because of missing values, the total data count is not identical for all parameters. The *P* for trend was calculated to assess how each parameter changes with decreasing eGFR levels.

Laboratory findings and urinalysis results

At the initial visit, the median serum creatinine and eGFR were 1.6 mg/dl and 30.0 ml/min per 1.73 m^2, respectively (Table 1). The absence of elevated creatine kinase levels argued against rhabdomyolysis as a cause of kidney dysfunction (Table 1).

Lower serum potassium, phosphorus, uric acid, and bicarbonate levels were observed in the patients, exhibiting a laboratory abnormality pattern characteristic of Fanconi syndrome (Table 1). Paradoxically, serum potassium levels were lower in patients with lower eGFR levels. Urinalysis findings were also consistent with those of Fanconi syndrome, with glycosuria observed in 79.5% of the patients. Urinary β2-microglobulin and urinary protein-to-creatinine ratio levels showed a significant trend across eGFR tertiles, with higher values observed in patients with lower eGFR.

Kidney biopsy findings

A total of 102 patients underwent kidney biopsy, and most biopsies were performed between January and March 2024 (Table 2). The timing of biopsies showed a significant trend across the eGFR tertiles ($P < 0.001$).

Light microscopy showed predominant tubulointerstitial changes, with tubulointerstitial nephritis in 50.0% and tubular necrosis in 32.0% of the cases. Notably, the prevalence of tubular necrosis showed a significant trend across eGFR tertiles, with higher frequencies observed in patients with lower eGFR. The glomerular changes were less prominent (Table 2). Minor glomerular abnormalities were the most frequent glomerular findings, present in 13.0% of cases. Other glomerular pathologies, including focal segmental glomerulosclerosis, endocapillary proliferative glomerulonephritis, mesangial proliferative glomerulonephritis, and diabetic nephropathy, were observed in ≈2% of cases. Glomerular lesions were not mentioned in ≈80% of the cases, suggesting that the glomeruli were intact in these cases.

Representative histopathologic findings in kidney biopsy specimens from a patient with Beni-koji tablet–associated kidney injury, including hematoxylin and eosin, periodic acid–Schiff, periodic acid–methenamine silver, and elastica Masson staining, are shown in Supplementary Figure S1. Immunofluorescence studies of the patient revealed decreased expression of proximal tubular transporters, including the apical membrane proteins megalin and sodium-glucose cotransporter 2, and related to b0,+ amino acid transporter, which are essential for the reabsorption of filtered substances (Supplementary Figure S2). The basolateral sodium-potassium adenosine triphosphatase α1 subunit, which is crucial for sodium cotransporter function, also showed reduced expression in proximal tubular cells.[18] In contrast, sodium-potassium adenosine triphosphatase α1 subunit expression was relatively preserved in connecting segments and thick ascending limbs of Henle, where the protein showed cytoplasmic staining patterns.[18] This selective pattern of injury, predominantly affecting proximal tubules while sparing other nephron segments, suggests that proximal tubules are the primary target of Beni-koji tablet–associated kidney injury.

Electron microscopic findings, available for 85 patients, showed tubular abnormalities in 49.4% of cases (Table 2). Glomerular findings on electron microscopy were less common, being observed in 10.6% of cases. Considering the relatively high levels of proteinuria observed in the initial survey, we sought to determine whether the proteinuria was of tubular or glomerular origin. To this end, we included additional questions regarding glomerular electron microscopy findings in the follow-up survey. Supplementary data were collected for 53 patients. Foot process effacement, a finding often associated with glomerular proteinuria, was

Table 2 | Kidney biopsy findings stratified by eGFR levels at initial visit

Parameter (n: all, low/medium/high eGFR tertile)	All	Tertile of eGFR at the initial visit			P_{trend}
		Low	Medium	High	
Reported kidney biopsy findings in the initial survey (102, 40/37/25)					
Month of kidney biopsy (102, 40/37/25)					<0.001
November 2023	1 (1.0)	1 (2.5)	0 (0.0)	0 (0.0)	
December 2023	6 (5.9)	2 (5.0)	4 (10.8)	0 (0.0)	
January 2024	17 (16.7)	10 (25.0)	5 (13.5)	2 (8.0)	
February 2024	22 (21.6)	12 (30.0)	8 (21.6)	2 (8.0)	
March 2024	37 (36.3)	15 (37.5)	14 (37.8)	8 (32.0)	
April 2024	19 (18.6)	0 (0.0)	6 (16.2)	13 (52.0)	
Light microscopic findings (100, 38/37/25)[a]					
Tubulointerstitial findings					
Tubulointerstitial nephritis	50 (50.0)	21 (55.3)	18 (48.6)	11 (44.0)	0.371
Tubular necrosis	32 (32.0)	17 (44.7)	12 (32.4)	3 (12.0)	0.007
Tubular injury[b]	20 (20.0)	6 (15.8)	7 (18.9)	7 (28.0)	0.250
Glomerular findings					
Minor glomerular abnormalities	13 (13.0)	2 (5.3)	7 (18.9)	4 (16.0)	0.161
Focal segmental glomerulosclerosis	2 (2.0)	1 (2.6)	0 (0.0)	1 (4.0)	0.813
Endocapillary proliferative glomerulonephritis	2 (2.0)	1 (2.6)	0 (0.0)	1 (4.0)	0.868
Mesangial proliferative glomerulonephritis	2 (2.0)	1 (2.6)	0 (0.0)	1 (4.0)	0.813
Diabetic nephropathy	1 (1.0)	0 (0.0)	1 (2.7)	0 (0.0)	0.813
Resulting unattached	2 (2.0)	0 (0.0)	1 (2.7)	1 (4.0)	0.250
Electron microscopic findings (85, 30/31/24)[c]					
Tubular findings	42 (49.4)	17 (56.7)	16 (51.6)	9 (37.5)	0.169
Glomerular findings	9 (10.6)	2 (6.7)	5 (16.1)	2 (8.3)	0.778
No significant findings	12 (14.1)	4 (13.3)	5 (16.1)	3 (12.5)	0.952
Resulting unattached	24 (28.2)	7 (23.3)	7 (22.6)	10 (41.7)	0.154
Electron microscopic findings except tubular findings in additional survey (53, 21/19/13)[a,d]					
Foot process effacement	13 (24.5)	4 (19.0)	5 (26.3)	4 (30.8)	0.426
Abnormal glomerular basement membrane	7 (13.2)	5 (23.8)	2 (10.5)	0 (0.0)	0.042
Abnormal endothelial cells (swollen or detached)	7 (13.2)	3 (14.3)	2 (10.5)	2 (15.4)	0.977
Presence of immune complexes	1 (1.9)	0 (0.0)	0 (0.0)	1 (7.7)	0.140
No significant findings	28 (52.8)	11 (52.4)	11 (57.9)	6 (46.2)	0.787

eGFR, estimated glomerular filtration rate.
[a]Multiple choice allowed.
[b]"Tubular injury" was added to the analysis based on frequent mentions in free-text comments, despite not being a predefined option in the survey questionnaire.
[c]These findings represent a summary of free-text comments provided by respondents regarding electron microscopy observations.
[d]These items were added in the follow-up survey to investigate glomerular findings, prompted by the discovery of relatively high proteinuria levels in the initial survey.
This table presents kidney biopsy findings for the entire study population ("All" column) and stratified by eGFR tertiles at the initial visit. The *P* for trend was calculated to assess how each parameter changes with decreasing eGFR levels. Data are presented as n (%).

the most common observation (24.5%), followed by abnormal glomerular basement membrane and abnormal endothelial cells (13.2%). However, more than half of patients (52.8%) showed no significant glomerular findings on electron microscopy (Table 2). These results suggest that although some cases exhibited glomerular changes that could contribute to proteinuria, the lack of significant glomerular findings in most cases supports the hypothesis that the observed proteinuria is predominantly of tubular origin, which is consistent with the overall picture of Beni-koji tablet–associated tubulointerstitial nephropathy.

To further investigate the origin of proteinuria, we examined the relationship between the markers of Fanconi syndrome and proteinuria and observed a significant inverse correlation between the natural logarithm of urinary protein-to-creatinine ratio and the serum levels of potassium, phosphorus, and uric acid at initial diagnosis (Supplementary Figure S3). This pattern suggests that the severity of Fanconi syndrome is associated with the level of proteinuria and may provide evidence that the observed proteinuria is primarily of tubular rather than glomerular origin. As expected, similar correlations were observed between natural logarithm of urinary β2-microglobulin and the serum levels of potassium and uric acid at initial diagnosis.

Treatment interventions

Treatment strategies were tailored to the severity of kidney dysfunction, with the primary intervention being discontinuation of Beni-koji tablets. As shown in Supplementary

Table 3 | Changes in key laboratory parameters from initial visit to last observation

	Initial visit		Last observation	
Parameter	n	Values	n	Values
Creatinine, mg/dl[a]	192	1.6 (1.2–2.5)	103	1.1 (0.9–1.3)
eGFR, ml/min per 1.73 m^2[a]	192	30.0 (17.2–42.4)	100	46.0 (39.1–54.0)
Low eGFR, <60 ml/min per 1.73 m^2[b]	192	183 (95.3)	100	87 (87.0)
Potassium, mEq/l[a]	192	3.5 (3.0–3.9)	102	4.1 (3.8–4.3)
Hypokalemia, <3.5 mEq/l[b]	192	90 (46.9)	102	7 (6.9)
Uric acid, mg/dl[b]	189	1.8 (1.4–2.9)	102	3.8 (2.8–4.6)
Hypouricemia, <2.0 mg/dl[b]	189	106 (56.1)	102	7 (6.9)
Phosphorus, mg/dl[a]	170	2.1 (1.6–2.9)	93	3.4 (2.9–3.6)
Hypophosphatemia, <2.5 mg/dl[b]	170	112 (65.9)	93	10 (10.8)
Bicarbonate ion, mEq/l[a]	137	18.2 (15.5–22.3)	65	26.3 (25.0–28.4)
Metabolic acidosis, <18.0 mmol/l[b]	137	64 (46.7)	65	0 (0)
UPCR, g/gCre[a]	177	1.64 (0.76–2.60)	95	0.11 (0.07–0.20)
Urine glucose[b]	190		97	
Negative or trace		39 (20.5)		97 (100.0)
1+		18 (9.5)		0 (0)
2+		16 (8.4)		0 (0)
3+		117 (61.6)		0 (0)

eGFR, estimated glomerular filtration rate; UPCR, urinary protein-to-creatinine ratio.
[a]Continuous variables are presented as median (interquartile range).
[b]Categorical variables are presented as number (percentage).
This table presents changes in key laboratory parameters from the initial visit to the last observation. The "Initial visit" columns show data at the time of initial presentation, whereas the "Last observation" columns display the most recent follow-up data available. The number of patients for each parameter is provided, as some patients may have missing data or were lost to follow-up. For each parameter, both the absolute values and the prevalence of clinically significant abnormalities (e.g., hypokalemia, hypouricemia) are shown. The reduction in sample size from initial visit to last observation reflects patients lost to follow-up or missing data. The last observation timing varied among patients and represents the most recent data available for each individual.

Table S4, most patients discontinued the product, with a notable increase in discontinuations from November 2023, peaking in March 2024, following the voluntary recall announcement.

Corticosteroid therapy was initiated in 34 patients (17.7%), with a significant trend across eGFR tertiles showing higher frequency of treatment in patients with lower eGFR (Table 1), indicating its use primarily in more severe cases. Hemodialysis was required in 6 patients (3.1%), all of whom were in the low eGFR tertile. Additional supportive treatments, as reported in the free-text responses, included potassium and/or phosphate repletion, bicarbonate administration, and antihypertensive medications.

Clinical course

Our study revealed that laboratory abnormalities characteristic of Fanconi syndrome improved significantly from the initial visit to the last observation (Table 3). Hypokalemia (<3.5 mEq/l) decreased from 46.9% to 6.9%, hypophosphatemia (<2.5 mg/dl) decreased from 65.9% to 10.8%, and hypouricemia (<2.0 mg/dl) decreased from 56.1% to 6.9%. Metabolic acidosis, initially present in 46.7% of the patients, was completely resolved. Glycosuria, initially present in 79.5% of the patients, was also completely resolved by time of the last observation. The median urinary protein-to-creatinine ratio decreased markedly from 1.64 to 0.11 g/g creatinine.

Kidney function showed notable improvements over time, reflecting the positive impact of discontinuing Beni-koji tablets and subsequent medical management (Figure 2a and b). However, 87.0% of patients still exhibited an eGFR of <60 ml/min per 1.73 m^2 in the follow-up survey (Table 3). Mixed-effects models for repeated measures analysis revealed a significant interaction between initial kidney function and time ($P < 0.001$), indicating a marked improvement in eGFR in patients with severe kidney impairment (Figure 2c). Intriguingly, our analysis showed that corticosteroid therapy, often used for various kidney disorders, did not significantly alter the trajectory of eGFR improvement ($P = 0.887$; Figure 2d). However, this finding should be interpreted with caution because of the small sample size of corticosteroid-treated patients (Table 1).

Among the 6 patients requiring hemodialysis, 1 presented with a unique profile. The patient was diagnosed with hydronephrosis on admission. Although the duration of hydronephrosis is unclear, this comorbidity likely contributed to the complexity of the case and the need for dialysis. One death occurred during the follow-up period; detailed information is provided in the Supplementary Information.

DISCUSSION

Our comprehensive nationwide survey identified a significant association between Beni-koji tablet use and the development of kidney dysfunction. These findings revealed a complex nephrotoxic effect characterized by features of Fanconi

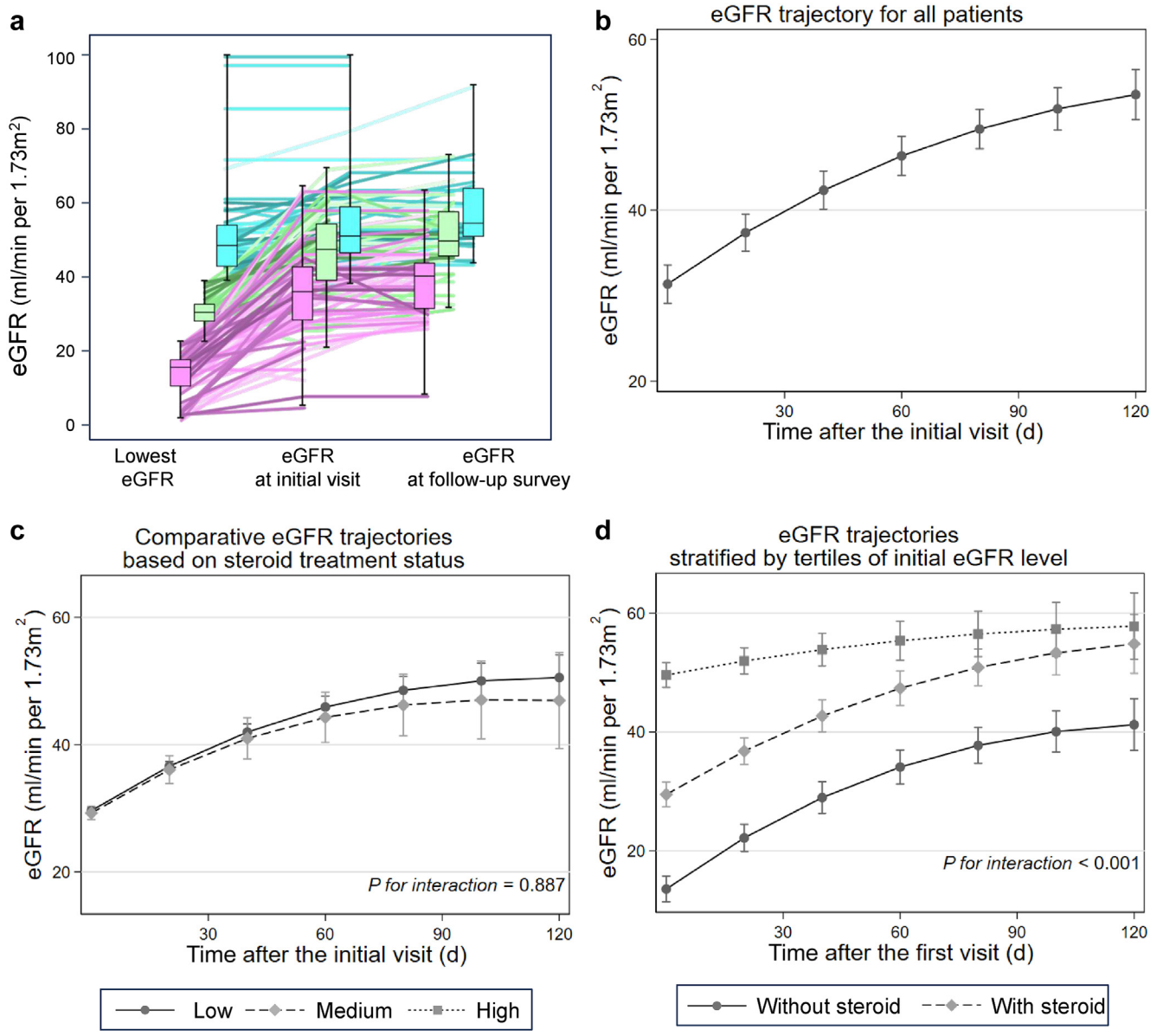

Figure 2 | Temporal changes in estimated glomerular filtration rate (eGFR) following discontinuation of Beni-koji tablets. (**a**) Spaghetti plot showing individual eGFR trajectories for all patients at 3 time points: lowest eGFR, initial survey, and follow-up survey. Data are color coded by tertiles of eGFR. Box plots represent the median and interquartile range for each tertile at each time point. (**b**) eGFR trajectory for all patients over time, estimated using a mixed-effects model. The dots represent the median values, and the error bars indicate the 95% confidence interval at specific time points. (**c**) eGFR trajectories stratified by eGFR tertiles, estimated using a mixed-effects model. Dots represent the median for each tertile, with error bars indicating the 95% confidence interval. *P* value for interaction between time and eGFR tertiles is shown. (**d**) Comparative eGFR trajectories based on corticosteroid treatment status, estimated using a mixed-effects model. Dots represent the median eGFR for each group (steroid-treated and non–steroid-treated), with error bars indicating the 95% confidence interval at specific time points.

syndrome, with a high prevalence of low eGFR (95.3%). This study expands on 4 previously reported case reports and case series,[19–23] offering a more comprehensive understanding of the scope and nature of this adverse effect.

Although our study lacks data on the baseline eGFR of patients before they started taking Beni-koji tablets, our results can be compared with those of a large-scale observational study of Japanese adults who participated in annual specific health checkups.[24,25] This population-based cohort study demonstrated that the prevalence of reduced eGFR (<60 ml/min per 1.73 m^2) in the general Japanese population increases with age: <5% in the 40 to 49 years age group, 5% to 10% in the 50 to 59 years age group, and 10% to 20% in the 60 to 69 years age group. Comparing these figures with our findings, it is evident that kidney function in our cohort remained substantially lower than what would be expected in the general Japanese population.

The temporal relationship strongly suggests a causal link; however, further investigation is still necessary to definitively prove causality. Citrinin, a well-known mycotoxin produced by red yeast rice, was ruled out as a potential cause in this case because the red yeast strain used in these products has been proven to be genetically incapable of producing this compound.[9]

Recent investigations by researchers at the National Institute of Health Sciences of Japan and collaborators have identified the presence of puberulic acid and 2 novel compounds, Y and Z, in the implicated product batches.[26] Importantly, *Penicillium adametzioides*, a blue mold, was detected in the Beni-koji production facility, introducing a new dimension to the investigation. This finding is significant because although red yeast rice itself is not capable of producing puberulic acid, *P adametzioides* can synthesize this compound. Furthermore, compound Y is postulated to be a modified form of monacolin K, likely resulting from the interaction between red yeast rice and blue mold.

To further elucidate the potential nephrotoxicity of these compounds, researchers at the National Institute of Health Sciences of Japan and collaborators conducted a 7-day rat study examining the individual effects of the following: (i) puberulic acid alone, (ii) compound Y alone, and (iii) compound Z alone. As reported by the Japanese Ministry of Health, Labor and Welfare, this study revealed that puberulic acid alone induced degeneration and necrosis in the proximal tubules, whereas no significant kidney toxicity was observed with compound Y or Z (Supplementary Figure S4). However, it is crucial to note that this rat study has not been published in a peer-reviewed scientific journal, and detailed experimental conditions and comprehensive results are currently available only through government reports, underscoring the need for further scientific scrutiny.

This study has 4 main limitations. First, as this was an observational study based on voluntary reporting through a nationwide survey, it may not have captured all the cases of Beni-koji tablet–associated kidney dysfunction. Second, the observation period was relatively short and varied among the patients, ranging from several weeks to several months. Third, a significant portion of patients lacked clear medical history data, which may limit our ability to fully account for preexisting conditions or risk factors. Fourth, the number of patients treated with corticosteroids was small, and the timing of corticosteroid initiation was not clearly defined, which limits our ability to draw definitive conclusions about the efficacy of corticosteroid treatment in this context. Despite these limitations, the large sample size and consistency of the findings across different clinical parameters provided valuable insights into the association between Beni-koji tablets and kidney dysfunction.

In conclusion, our study provides robust evidence of an association between specific Beni-koji tablets and kidney dysfunction. We observed significant improvement in Fanconi syndrome–related parameters following discontinuation of Beni-koji tablets. However, 87.0% of patients still showed eGFR <60 ml/min per 1.73 m^2 at the last observation, suggesting a potential for longer-term kidney effects that warrant further investigation. Furthermore, this incident emphasizes the necessity for more stringent safety evaluations of dietary supplements, particularly in relation to potential blue mold contamination of specific batches during the manufacturing process. Therefore, it is imperative to conduct more detailed toxicological studies, investigate production processes, and establish stringent quality control measures to prevent similar incidents. These efforts are crucial to ensure the safety of dietary supplements and protect public health.

APPENDIX

Collaborators

Ageo Central General Hospital, Masami Ono; Akashi Medical Center, Department of Medicine, Yuriko Yonekura; Anzu Clinic Asakusabashi, Yuki Nishizawa; Azuma Kidney Clinic, Masahiro Azuma; Chiba Tokushukai Hospital, Ryousuke Aoki; Chutoen General Medical Center, Koji Inagaki; Hirosaki University Graduate School of Medicine, Daiki Nagawa; Ehime University Graduate School of Medicine, Ken-ichi Miyoshi; Fukui-ken Saiseikai Hospital, Yasutaka Kamikawa; Minamitama Hospital, Yuri Kasagi; Kawasaki Medical School, Seiji Kishi; Fujioka General Hospital, Shinsuke Motegi; Juntendo University Urayasu Hospital, Hitoshi Suzuki; Konan Medical Center, Shioko Okada; Kumamoto Chuo Hospital, Kazufumi Nomura; International University of Health and Welfare, Jun Ito; Japan Community Healthcare Organization (JCHO) Saitama Medical Center, Tomoaki Itoh; Kasugai Municipal Hospital, Yosuke Saka; Mito Saiseikai General Hospital, Itaru Ebihara; Nagoya City University Graduate School of Medical Sciences, Takayuki Hamano; Yuurinkouseikai Fuji Hospital, Makoto Ogi; National Hospital Organization (NHO) Chibahigashi National Hospital, Toshiyuki Imasawa; Omori Red Cross Hospital, Ken Shibuya; School of Medicine, Iwate Medical University, Kazuhiro Yoshikawa; Kawasaki Municipal Tama Hospital, Shu Ushimaru; Kobe University Graduate School of Medicine, Hideki Fujii; Juntendo Nerima Hospital, Koji Sato; Keio University School of Medicine, Kaori Hayashi; Niigata Prefectural Shibata Hospital, Niigata, Masato Habuka; Dokkyo Medical University, Akihiro Tojo; Ebina General Hospital, Hideyuki Katori; Eiju General Hospital, Akiko Torii; Fuji City General Hospital, Reina Miyazaki; Fukuoka Higashi Hobashira Clinic, Emi Kitashoji; Fukuyama City Hospital, Takehiko Tokura; Gengendo Kimitsu Hospital, Yoshikazu Nemoto; Gunma Saiseikai Maebashi Hospital, Masahito Baba; Hamanasu Clinic, Risshi Kudo; Harunohi Medical Clinic, Atsushi Saito; Higashiosaka City Medical Center, Ryuta Fujimura; Hino Municipal Hospital, Takashi Araki; Hiraku Clinic, Hiraku Yoshida; Hiratsuka Kyosai Hospital, Takanori Miyazaki; Hiroshima University Hospital, Yosuke Osaki; Hokkaido University Hospital, Saori Nishio; Hoya Clinic, Yasunori Utsunomiya; Hyogo Prefectural Harima-Himeji General Medical Center, Shohei Nakanishi; Ichiyokai Harada Hospital, Toshiki Doi; Japan Community Healthcare Organization Sendai Hospital, Mitsuhiro Sato; Japanese Red Cross Kumamoto Hospital, Yoei Miyabe; JR Sapporo Hospital, Hideaki Yoshida; Kagawa University, Tadashi Sofue; Kansai Rosai Hospital, Masaaki Izumi; Kawakita General Hospital, Matsuhiko Hayashi; Kitasato University Hospital, Togo Aoyama; Kobe City Medical Center General Hospital, Keisuke Osaki; Koga Hospital 21, Ryuuji Iwatani; Kyoto City Hospital, Noriyuki Iehara; Matsui Heart Clinic, Matsui Mikoto; Medical Research Institute Kitano Hospital, PIIF Tazuke-Kofukai, Tatsuo Tsukamoto; Nara City Hospital, Yoshiharu Nishitani; Osaka City General Hospital, Yoshio Konishi; Osaka University, Shihomi Maeda and Yuki Kawano; Okayama Saiseikai General Hospital, Keisuke Maruyama; Otemae Hospital, Aya

Nakamori; Saiseikai General Hospital Department of Nephrology, Eiji Ishikawa; Saiseikai Shiga Hospital, Norihisa Osawa; Saiseikai Tondabayashi Hospital/Department of Nephrology, Masami Komeda; Sanai Memorial Soga Clinic, Ritsuko Hasegawa; Sapporo City General Hospital, Satoka Shiratori-Aso; Seiwa-Clinic, Sachiko Takahashi; Sendai-Makinose Urology-Nephrology Clinic, Hiroyuki Deguchi; Shimbashiaoki Clinic, Toshiyuki Aoki; Shonan Kamakura General Hospital, Shuzo Kobayashi; St. Marianna University School of Medicine, Daisuke Ichikawa; Takamatsu Red Cross Hospital, Tomoko Yokoyama; Takashima Municipal Hospital, Tetsuya Nagae; Takeru Clinic, Takayuki Sakai; Teikyo University Hospital, Shigeru Shibata; Toda Central General Hospital, Jun Ino; Tokushima Red Cross Hospital, Motokazu Matsuura; Tokyo Medical University Hospital, Rieko China; Tokyo Metropolitan Police Hospital, Tomonari Okada; Toyama Machinaka Hospital, Maiko Ohara; Toyama Rosai Hospital, Hiroyuki Kinuno; Tsuchiura Kyodo General Hospital, Takayuki Toda; Yamanashi Prefectural Central Hospital, Ikuo Nukui; Yokohama Sakae Kyosai Hospital, Jin Oshikawa; and other survey participants.

DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

The data that support the findings of this study are included in this article, and all other supporting data are available on request from the corresponding author, YI. The data are not publicly available because of the privacy of participants or ethical restrictions.

ACKNOWLEDGMENTS

We would like to express our sincere gratitude to all the physicians who generously dedicated their time and effort in responding to this survey:

Ageo Central General Hospital, Masami Ono; Akashi Medical Center, Department of Medicine, Yuriko Yonekura; Anzu Clinic Asakusabashi, Yuki Nishizawa; Azuma Kidney Clinic, Masahiro Azuma; Chiba Tokushukai Hospital, Ryousuke Aoki; Chutoen General Medical Center, Koji Inagaki; Hirosaki University Graduate School of Medicine, Daiki Nagawa; Ehime University Graduate School of Medicine, Ken-ichi Miyoshi; Fukui-ken Saiseikai Hospital, Yasutaka Kamikawa; Minamitama Hospital, Yuri Kasagi; Kawasaki Medical School, Seiji Kishi; Fujioka General Hospital, Shinsuke Motegi; Juntendo University Urayasu Hospital, Hitoshi Suzuki; Konan Medical Center, Shioko Okada; Kumamoto Chuo Hospital, Kazufumi Nomura; International University of Health and Welfare, Jun Ito; Japan Community Healthcare Organization (JCHO) Saitama Medical Center, Tomoaki Itoh; Kasugai Municipal Hospital, Yosuke Saka; Mito Saiseikai General Hospital, Itaru Ebihara; Nagoya City University Graduate School of Medical Sciences, Takayuki Hamano; Yuurinkouseikai Fuji Hospital, Makoto Ogi; National Hospital Organization (NHO) Chibahigashi National Hospital, Toshiyuki Imasawa; Omori Red Cross Hospital, Ken Shibuya; School of Medicine, Iwate Medical University, Kazuhiro Yoshikawa; Kawasaki Municipal Tama Hospital, Shu Ushimaru; Kobe University Graduate School of Medicine, Hideki Fujii; Juntendo Nerima Hospital, Koji Sato; Keio University School of Medicine, Kaori Hayashi; Niigata Prefectural Shibata Hospital, Niigata, Masato Habuka; Dokkyo Medical University, Akihiro Tojo; Ebina General Hospital, Hideyuki Katori; Eiju General Hospital, Akiko Torii; Fuji City General Hospital, Reina Miyazaki; Fukuoka Higashi Hobashira Clinic, Emi Kitashoji; Fukuyama City Hospital, Takehiko Tokura; Gengendo Kimitsu Hospital, Yoshikazu Nemoto; Gunma Saiseikai Maebashi Hospital, Masahito Baba; Hamanasu Clinic, Risshi Kudo; Harunohi Medical Clinic, Atsushi Saito; Higashiosaka City Medical Center, Ryuta Fujimura; Hino Municipal Hospital, Takashi Araki; Hiraku Clinic, Hiraku Yoshida; Hiratsuka Kyosai Hospital, Takanori Miyazaki; Hiroshima University Hospital, Yosuke Osaki; Hokkaido University Hospital, Saori Nishio; Hoya Clinic, Yasunori Utsunomiya; Hyogo Prefectural Harima-Himeji General Medical Center, Shohei Nakanishi; Ichiyokai Harada Hospital, Toshiki Doi; Japan Community Healthcare Organization Sendai Hospital, Mitsuhiro Sato; Japanese Red Cross Kumamoto Hospital, Yoei Miyabe; JR Sapporo Hospital, Hideaki Yoshida; Kagawa University, Tadashi Sofue; Kansai Rosai Hospital, Masaaki Izumi; Kawakita General Hospital, Matsuhiko Hayashi; Kitasato University Hospital, Togo Aoyama; Kobe City Medical Center General Hospital, Keisuke Osaki; Koga Hospital 21, Ryuuji Iwatani; Kyoto City Hospital, Noriyuki Iehara; Matsui Heart Clinic, Matsui Mikoto; Medical Research Institute Kitano Hospital, PIIF Tazuke-Kofukai, Tatsuo Tsukamoto; Nara City Hospital, Yoshiharu Nishitani; Osaka City General Hospital, Yoshio Konishi; Osaka University, Shihomi Maeda and Yuki Kawano; Okayama Saiseikai General Hospital, Keisuke Maruyama; Otemae Hospital, Aya Nakamori; Saiseikai General Hospital Department of Nephrology, Eiji Ishikawa; Saiseikai Shiga Hospital, Norihisa Osawa; Saiseikai Tondabayashi Hospital/Department of Nephrology, Masami Komeda; Sanai Memorial Soga Clinic, Ritsuko Hasegawa; Sapporo City General Hospital, Satoka Shiratori-Aso; Seiwa-Clinic, Sachiko Takahashi; Sendai-Makinose Urology-Nephrology Clinic, Hiroyuki Deguchi; Shimbashiaoki Clinic, Toshiyuki Aoki; Shonan Kamakura General Hospital, Shuzo Kobayashi; St. Marianna University School of Medicine, Daisuke Ichikawa; Takamatsu Red Cross Hospital, Tomoko Yokoyama; Takashima Municipal Hospital, Tetsuya Nagae; Takeru Clinic, Takayuki Sakai; Teikyo University Hospital, Shigeru Shibata; Toda Central General Hospital, Jun Ino; Tokushima Red Cross Hospital, Motokazu Matsuura; Tokyo Medical University Hospital, Rieko China; Tokyo Metropolitan Police Hospital, Tomonari Okada; Toyama Machinaka Hospital, Maiko Ohara; Toyama Rosai Hospital, Hiroyuki Kinuno; Tsuchiura Kyodo General Hospital, Takayuki Toda; Yamanashi Prefectural Central Hospital, Ikuo Nukui; Yokohama Sakae Kyosai Hospital, Jin Oshikawa; and other survey participants.

AUTHOR CONTRIBUTIONS

MS carried out conceptualization, resources, data curation, formal analysis, investigation, methodology, validation, visualization, and writing (original draft); IM carried out conceptualization, resources, formal analysis, investigation, methods, visualization, and writing (review and editing); YD carried out conceptualization, resources, formal analysis, investigation, methods, and writing (review and editing); AM carried out investigation, visualization, and writing (review and editing); AT carried out resources; MN carried out writing (review and editing) and supervision; YI carried out conceptualization, investigation, writing (review and editing), project administration, and supervision.

Supplementary material is available online at www.kidney-international.org.

REFERENCES

1. Gabardi S, Munz K, Ulbricht C. A review of dietary supplement-induced renal dysfunction. *Clin J Am Soc Nephrol*. 2007;2:757–765.
2. Knapik JJ, Trone DW, Steelman RA, et al. Adverse effects associated with use of specific dietary supplements: the US Military Dietary Supplement Use Study. *Food Chem Toxicol*. 2022;161:112840.
3. Nauffal M, Gabardi S. Nephrotoxicity of natural products. *Blood Purif*. 2016;41:123–129.
4. Geller AI, Shehab N, Weidle NJ, et al. Emergency department visits for adverse events related to dietary supplements. *N Engl J Med*. 2015;373:1531–1540.
5. Palmer ME, Haller C, McKinney PE, et al. Adverse events associated with dietary supplements: an observational study. *Lancet*. 2003;361:101–106.

6. Sato K, Kodama K, Sengoku S. Optimizing the relationship between regulation and innovation in dietary supplements: a case study of food with function claims in Japan. *Nutrients*. 2023;15:476.
7. Tanemura N, Machii Y, Urushihara H. The first survey of gap between the actual labelling and efficacy information of functional substances in food under the regulatory processes in Japan. *J Functional Foods*. 2020;72:104047.
8. Matsumoto C, Tomiyama H, Takahashi O, et al. An evidence review project for food with function claims ～challenges of the Japan Society for Vascular Failure for the promotion of adequate evidences for food with function claims. *Hypertens Res*. 2024;47:533–536.
9. Higa Y, Kim YS, Altaf-Ul-Amin M, et al. Divergence of metabolites in three phylogenetically close Monascus species (M. pilosus, M. ruber, and M. purpureus) based on secondary metabolite biosynthetic gene clusters. *BMC Genomics*. 2020;21:679.
10. Younes M, Aggett P, Aguilar F, et al. Scientific opinion on the safety of monacolins in red yeast rice. *Efsa J*. 2018;16:e05368.
11. Fukami H, Higa Y, Hisano T, et al. A review of red yeast rice, a traditional fermented food in Japan and East Asia: its characteristic ingredients and application in the maintenance and improvement of health in lipid metabolism and the circulatory system. *Molecules*. 2021;26:1619.
12. Zhang Y, Chen Z, Wen Q, et al. An overview on the biosynthesis and metabolic regulation of monacolin K/lovastatin. *Food Funct*. 2020;11:5738–5748.
13. Marcheluzzo S, Faggian M, Zancato M, et al. Analysis of monacolins and berberine in food supplements for lipid control: an overview of products sold on the Italian market. *Molecules*. 2021;26:2222.
14. National Center for Complimentary and Integrative Health. Red yeast rice: what you need to know. Accessed June 1, 2024. https://www.nccih.nih.gov/health/red-yeast-rice
15. Flajs D, Peraica M. Toxicological properties of citrinin. *Arh Hig Rada Toksikol*. 2009;60:457–464.
16. Ministry of Health Law. Information on adverse events associated with Beni-koji (red yeast rice) related products. Accessed June 1, 2024. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/shokuhin/daietto/index_00005.html
17. Oka T, Sakaguchi Y, Hattori K, et al. Mineralocorticoid receptor antagonist use and hard renal outcomes in real-world patients with chronic kidney disease. *Hypertension*. 2022;79:679–689.
18. Sabolić I, Herak-Kramberger CM, Breton S, et al. Na/K-ATPase in intercalated cells along the rat nephron revealed by antigen retrieval. *J Am Soc Nephrol*. 1999;10:913–922.
19. Murata Y, Hemmi S, Akiya Y, et al. Certain red yeast rice supplements in Japan cause acute tubulointerstitial injury. *Kidney Int Rep*. 2024;9:2824–2828.
20. Maiguma M, Kihara M, Hamaguchi M, et al. Successful treatment of acute tubulointerstitial nephritis probably due to Benikoji CholesteHelp(®), a supplement containing red yeast rice. *CEN Case Rep*. Published online June 17, 2024. https://doi.org/10.1007/s13730-024-00897-9
21. Miyazaki R, Takahashi Y, Kawamura T, et al. Acute kidney tubular injury after ingestion of red yeast rice supplement. *Clin Kidney J*. 2024;17:sfae151.
22. Oda K, Murata T, Tanaka F, et al. A case of acute kidney injury and Fanconi syndrome while taking multiple supplements, including Red Yeast Rice Cholesterol Help(®). *CEN Case Rep*. Published online June 20, 2024. https://doi.org/10.1007/s13730-024-00903-0
23. Kawai Y, Ozawa M, Isomura A, et al. A case of Fanconi syndrome that developed following a year of consumption of a red yeast rice supplement. *CEN Case Rep*. Published online July 10, 2024. https://doi.org/10.1007/s13730-024-00913-y
24. Imai E, Horio M, Watanabe T, et al. Prevalence of chronic kidney disease in the Japanese general population. *Clin Exp Nephrol*. 2009;13:621–630.
25. Nagai K, Asahi K, Iseki K, et al. Estimating the prevalence of definitive chronic kidney disease in the Japanese general population. *Clin Exp Nephrol*. 2021;25:885–892.
26. Tanaka S, Masumoto N, Makino T, et al. Novel compounds isolated from health food products containing beni-koji (red yeast rice) with adverse event reports. *J Nat Med*. 2024;78:845–848.