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Acute Tubular Injury and Fanconi Syndrome Associated With Red Yeast Rice Supplement

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Received 18 October 2024; revised 2 December 2024; accepted 16 December 2024; published online 26 December 2024

Kidney Int Rep (2025) **10,** 956–959; https://doi.org/10.1016/j.ekir.2024.12.016

INTRODUCTION

In September 2023, reports from Japan linked the use of red yeast rice supplements (Benikoji CholesteHelp, Kobayashi Pharmaceutical Co., Osaka, Japan) with renal impairment, particularly tubulointerstitial dysfunction. Several individuals who consumed these supplements experienced notable kidney damage, including acute kidney injury (AKI) and Fanconi syndrome, both characterized by tubular dysfunction. Histopathological findings, such as vacuolization, flattening of proximal tubular cells, and mitochondrial swelling, were also observed in these cases.[1] It was hypothesized that the cause was not the red yeast rice itself but rather puberulic acid[2] produced by contaminated blue mold during the manufacturing process; however, the exact mechanisms remain unknown.

AKI is characterized by a rapid decline in renal function, often because of tubular injury resulting from severe energy depletion and mitochondrial dysfunction. Mitochondrial impairment triggers cell death through necrosis, apoptosis, or ferroptosis.[3] When damaged tubules are not adequately repaired, fibrosis may occur, leading to the progression of chronic kidney disease. Current therapeutic strategies aim to target mitochondrial dysfunction, oxidative stress, and impaired energy metabolism to prevent tubular injury and renal disease progression. In addition, the role of kidneys in systemic glucose regulation, particularly via gluconeogenesis, has been gaining increasing attention.[4] This report details 2 clinical cases of kidney injury associated with red yeast rice supplementation, characterized by Fanconi syndrome, acute tubular injury, and prominent glycogen accumulation. These cases underscore the importance of evaluating the safety of fermented supplements and their potential metabolic effects on kidney health.

CASE PRESENTATION

Case 1

A 60-year-old woman presented with renal dysfunction and abnormal urinalysis results. Her medical history included endometriosis, a left ovarian cyst, and appendicitis, without any family history of kidney disease. Previously, her renal function was normal; however, a recent test revealed elevated low-density lipoprotein cholesterol levels (169 mg/dl), leading to a diagnosis of dyslipidemia. Approximately 8 months earlier, she began taking red yeast rice supplements (Benikoji CholesteHelp, Lot X3017) for cholesterol control, which continued for 4 months. During this time, her blood pressure increased, requiring amlodipine (5 mg/d). She also noticed frothy urine indicative of proteinuria. Five days before her hospital visit, she became aware of reports linking the supplement to renal impairment, prompting her to stop taking it and consult her physician.

Initial laboratory tests revealed a serum creatinine (Cr) level of 1.56 mg/dl and a urine protein-to-Cr ratio of 1.72 g/g Cr, leading to referral for further evaluation and renal biopsy. Upon admission, her blood pressure was 161/91 mmHg, heart rate was 61 beats/min, and oxygen saturation was 99%. Physical examination was unremarkable; however, laboratory results confirmed renal dysfunction (serum Cr: 1.39 mg/dl and estimated glomerular filtration rate: 30.9 ml/min per 1.73 m^2), hypokalemia (3.3 mEq/l), hypophosphatemia (1.9 mg/dl), and hypouricemia (1.8 mg/dl). Autoimmune markers were negative. Urinalysis revealed proteinuria and glucosuria, without hematuria. A spot urine protein-to-Cr ratio was 1.51 g/g Cr, and β2-microglobulin was elevated (10,454 μg/l), with a high N-acetyl-β-D-glucosaminidase index (40.46 U/g Cr).

Postadmission tests revealed pan-aminoaciduria and additional markers of tubulointerstitial dysfunction, consistent with Fanconi syndrome and AKI. Sodium restriction and calcium channel blocker therapy were initiated; however, her hypertension persisted and telmisartan (40 mg/d) was added.

Case 2

A 58-year-old man with a history of hypertension presented with proteinuria and worsened renal function. He had been on amlodipine (5 mg/d) for several years and routinely underwent blood and urine tests, which had shown normal serum Cr levels (0.99 mg/dl) and no proteinuria 7 months earlier. Two months before presentation, he started taking red yeast rice supplements (Benikoji CholesteHelp, Lot X3017) to manage elevated low-density lipoprotein cholesterol. After a month, the supplement was discontinued because of severe fatigue, which worsened alongside foamy urine and a 3 kg weight loss. He visited his primary care physician, who observed elevated serum Cr (2.28 mg/dl) and proteinuria (2+), leading to a referral for a renal biopsy.

Upon admission, the laboratory findings confirmed renal dysfunction (serum Cr 1.65 mg/dl), hypophosphatemia (1.9 mg/dl), hypouricemia (UA: 1.8 mg/dl), and proteinuria (0.89 g/gCr). β2-microglobulin was significantly elevated (17,898 μg/l), and the N-acetyl-β-D-glucosaminidase index was high (26.7 U/g Cr). Phosphate reabsorption was reduced (51.3%), and excessive urinary glucose excretion (8 g/d) was observed, suggesting tubulointerstitial nephritis with Fanconi syndrome, likely induced by red yeast rice supplements. The clinical characteristics of the 2 cases are summarized in Supplementary Table S1.

Kidney Biopsy

Kidney biopsies from both patients revealed sporadic degenerative changes in the tubular epithelium without significant inflammatory infiltration of the tubules or interstitium (Figure 1a). Periodic acid–Schiff staining, with and without diastase digestion, revealed considerable glycogen accumulation in the tubular epithelium (Figure 1b–d, Supplementary Figures S1 and S2). Transmission electron microscopy and low vacuum electron microscopy confirmed the presence of glycogen granules surrounding the mitochondria (Figure 1e–i and Supplementary Figure S2).

Immunohistochemical analysis revealed a diffuse and marked reduction in glucose transporter 2 expression, whereas sodium glucose co-transporter 2 expression was relatively preserved (Supplementary Figure S3).

DISCUSSION

As of December 23, 2024, a report by the Ministry of Health, Labor and Welfare of Japan documented 1930 hospital visits attributed to kidney diseases, including 345 cases requiring hospitalization and 397 fatalities.[S1]

A PubMed search identified 12 case reports of AKI associated with red yeast rice supplements, specifically "Benikoji CholesteHelp" (Supplementary Table S2). Among these cases, 11 were diagnosed with Fanconi syndrome, whereas acute tubular injury or acute tubular necrosis was observed on light microscopy in the same number of cases.

A recent *Letter to the Editor* first reported glycogen accumulation in the proximal tubules as a distinctfinding.[5] Retrospective review of earlier studies revealed 2 reports describing "glycogen-like particles" in tubular epithelium in transmission electron microscopy images; however, these particles were not explicitly identified as glycogen by the respective authors.[6,7]

The findings in these 2 cases mirror the pathology observed in Fanconi-Bickel syndrome,[8] a rare disorder characterized by defective glucose and galactose transport because of mutations in the *SLC2A2* gene, which encodes glucose transporter 2. The reduction in glucose transporter 2 expression observed in our cases were diffuse; however, certain tubular segments retained their expression levels. This pattern was consistent with the histological findings of focal glycogen accumulation in specific tubules. The amelioration of glycogen accumulation through sodium glucose cotransporter 2 inhibitor administration in *GLUT2* knockout mice[9] may offer valuable insights into the underlying mechanisms.

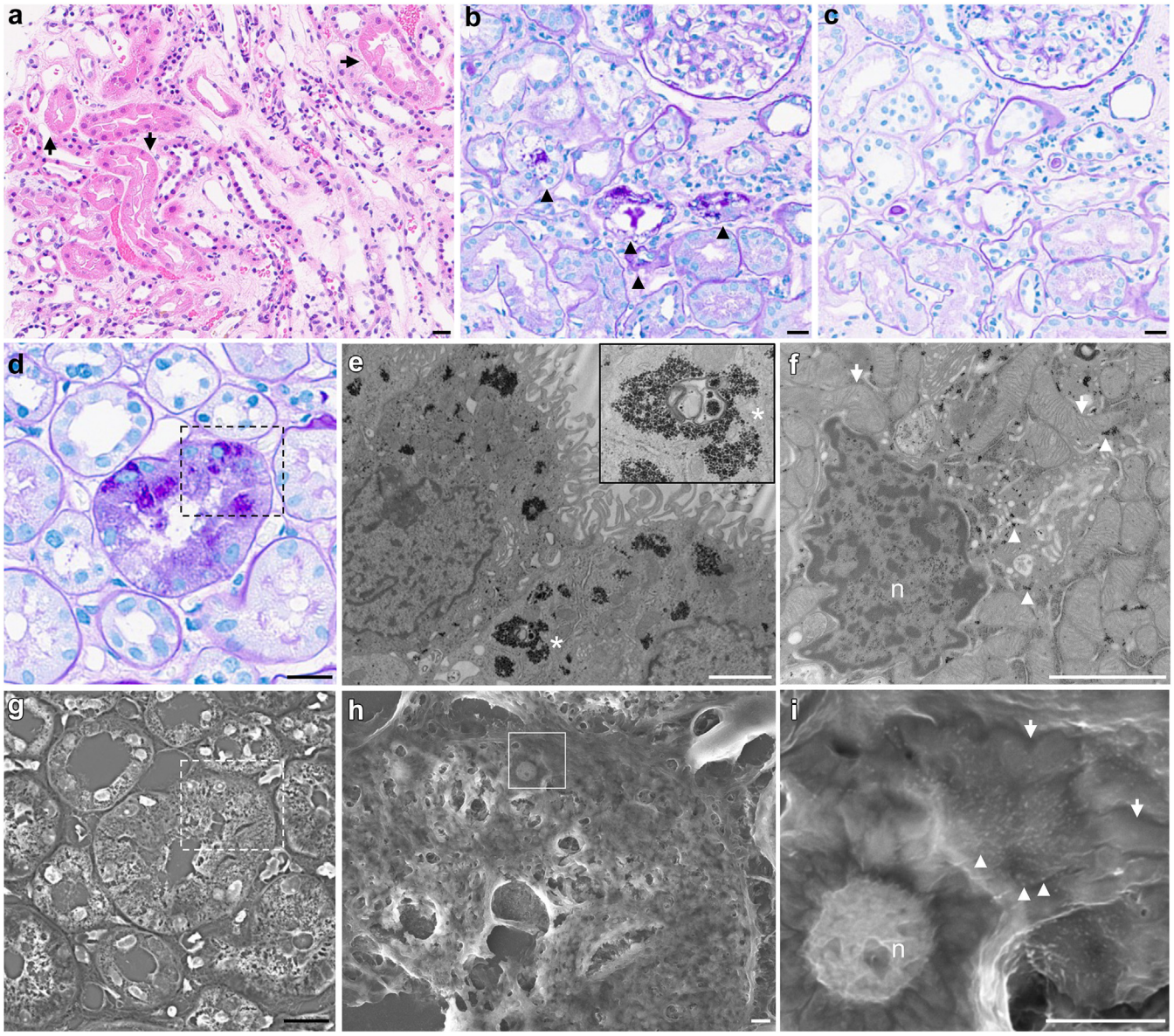

Figure 1. Pathological features of acute kidney injury associated with red yeast rice supplements. (a) Degenerative changes in the tubular epithelium are sporadically observed in hematoxylin and eosin staining (black arrows). Glycogen accumulation in the proximal tubular epithelium is detected using celloidin-embedded Periodic Acid–Schiff (PAS) staining (b) without or (c) with diastase digestion in serial sections (black arrowheads indicate glycogen deposits). (d) PAS staining highlights proximal tubules with prominent glycogen accumulation. (e) Transmission electron microscopy (TEM) reveals diffuse glycogen granules within the tubular epithelium (asterisks mark the same lesion), with a higher magnification (f) showing glycogen granules (arrowheads) localized around mitochondria (arrows). (g and h) Low vacuum scanning electron microscopy (SEM) images (secondary electron mode; Flex-1000, HITACHI, Japan) of the same PAS-stained section as in (d), treated with osmium, uranium, and lead, showing (g) an overview and (h) a magnified area. A further magnification (i) of the boxed region in (h) highlights glycogen granules (arrowheads) adjacent to mitochondria (arrows). Dotted squares indicate the same lesion across panels. Scale bars: black, 20 μm; white, 2.0 μm.

In conclusion, these cases underscore the importance of understanding the metabolic effects of dietary supplements on kidney health, particularly those involving fermented products (Table 1). The potential for contaminants to induce serious renal injury, including AKI and Fanconi syndrome, requires further research to elucidate the underlying mechanisms and establish regulatory guidelines for the safe use of such

Table 1. Teaching points

1.	Red yeast rice supplements (Benikoji CholesteHelp) have been associated with acute kidney injury presenting with Fanconi syndrome and acute tubular injury.
2.	Detailed histopathological analysis revealed significant glycogen accumulation, particularly surrounding the mitochondria, within the affected tubular epithelial cells.
3.	The observed diffuse and segmental depletion of GLUT2 in proximal tubules suggests a potential connection to glycogen accumulation, contributing to AKI in cases associated with red yeast rice supplement use.

AKI, acute kidney injury; GLUT2, glucose transporter 2.

supplements. Improved awareness of these risks may help to prevent future cases.

DISCLOSURE

All the authors declared no conflicting interests.

PATIENT CONSENT

Informed written consent was obtained from all participating patients.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.jp) for English language editing.

Funding

Funding for this study was from the Japan Agency for Medical Research and Development (AMED) (Grant Number JP23wm0325066) to Kunio K.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon request. No specific codes were used for data generation in this study.

AUTHOR CONTRIBUTIONS

MS, YK, KeK, and KuK contributed to the writing of the manuscript. Data collection and renal biopsy were performed by YK, KeK, MS, TM, FS, and TS. Pathological analyses were performed by MS, KuK, MB, and TT. MS, KuK, DK, TS, FK, KH, and HH discussed the results and contributed to the final manuscript. All the authors reviewed and approved the final version of the manuscript.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used GPT-4 (https://openai.com/index/gpt-4/) for language editing. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Reference.

Figure S1. Glycogen accumulation demonstrated by celloidin coating and Periodic Acid–Schiff (PAS) staining with and without diastase digestion in case 1.

Figure S2. Pathological features of acute kidney injury observed in case 2.

Figure S3. Immunohistochemical analysis of glucose transporter expression.

Table S1. Clinical laboratory findings, highlighting Fanconi syndrome.

Table S2. Literature review of acute kidney injury associated with red yeast rice supplements.

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