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Renal Impairment in Wilson's Disease

Zi-Wei Zheng[1,4], Meng-Hui Xu[1,4], Lu-Na Fan[1], Rou-Min Wang[1], Wan-Qing Xu[1], Guo-Min Yang[1], Ling-Yu Guo[1], Chuan Liu[1], Yi Dong[1] and Zhi-Ying Wu[1,2,3]

[1]Department of Medical Genetics and Center for Rare Diseases, Zhejiang Key Laboratory of Rare Diseases for Precision Medicine and Clinical Translation, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China; [2]Nanhu Brain-computer Interface Institute, Hangzhou, Zhejiang, China; and [3]MOE Frontier Science Center for Brain Science and Brain-machine Integration, School of Brain Science and Brain Medicine, Zhejiang University, Hangzhou, Zhejiang China

Correspondence: Zhi-Ying Wu, Department of Medical Genetics and Center for Rare Diseases, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang Key Laboratory of Rare Diseases for Precision Medicine and Clinical Translation, 88 Jiefang Road, Hangzhou 310009, China. E-mail: zhiyingwu@zju.edu.cn

[4]Z-WZ and M-HX contributed equally to this work and should be considered co–first authors.

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INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disorder caused by mutations in the *ATP7B* gene, resulting in copper accumulation, which predominantly affects the liver and brain.[1] Early diagnosis and treatment are crucial for achieving favorable outcomes, because delayed intervention can lead to increased mortality and disability.[2,3] Although renal involvement is uncommon as an initial symptom, it is more prevalent in children and may manifest as tubular dysfunction or glomerular injury because of copper deposition in renal tubules.[4]

Copper-chelation therapies, such as D-penicillamine and dimercaptosuccinic acid, are effective in reducing copper burden[5] but may occasionally cause kidney injury, characterized by proteinuria or hematuria.[6,7] Zinc, used as a maintenance therapy, prevents copper absorption with minimal renal impact. However, systematic studies on renal dysfunction in WD are limited. This study aims to investigate urinary abnormalities and renal function to evaluate the impact of different treatment regimens, assisting clinicians in early detection, especially in pediatric cases, and preventing misdiagnosis and irreversible renal damage.

RESULTS

Clinical Characteristics

The clinical baseline parameters for the patients with WD and controls are summarized in Supplementary Table S1. A total of 607 unrelated patients with WD were recruited in the study, whereas the control group comprised 709 unrelated individuals (Supplementary Figure S1). The detailed methods used for this study are presented in the Supplementary Methods.

Abnormal renal manifestations in patients with WD included hematuria (48.03% overall; 51.32% aged $<$ 18 years), similar to controls (49.25%, $P > 0.05$). Proteinuria was significantly higher in patients with WD (12.18%) than in the controls (4.65%, $P = 0.000$), including those aged $<$ 18 years (6.00%, $P = 0.005$). Glucosuria was more frequent in patients with WD (5.51%) than in controls (0.28%, $P = 0.000$). Renal markers (blood urea nitrogen, serum creatinine [SCr], uric acid, cystatin C, and beta-2 microglobulin) and urinary parameters, including occult blood, glucose, urobilinogen, and various cells, varied significantly between groups ($P < 0.05$), though urinary protein levels showed no significant difference ($P > 0.05$). Besides, there are significant differences in renal function and urine routine indexes in patients with hepatic, neurologic, and asymptomatic WD (Supplementary Table S2).

Treatment and Renal Outcome

There were significant differences in renal indices before treatment across groups, as shown in Table 1. Before treatment, significant differences were observed in SCr and uric acid levels among the groups ($P < 0.05$). Following intervention, blood urea nitrogen levels decreased in all groups, although not statistically significant ($P > 0.05$). SCr levels improved significantly in the zinc group ($P = 0.004$). Cystatin C levels showed significant reductions across all treatments ($P < 0.05$).

Table 1. Laboratory parameters before and after drug usage

Parameters	Zinc		DMSA		DPA	
Patients (*n*)	211		251		145	
Gender (male/female)	125/86		140/111		67/78	
	Before	After	Before	After	Before	After
Age (yrs)	12 (6–20)	13 (7–20)[a]	26 (19–33)	26 (21–33.5)[a]	27 (20–34)	29 (21–34)[a]
Abnormal renal findings, *n* (%)						
Proteinuria	4 (3.5)	4 (3.5)[a]	38 (16.5)	35 (15.2)[a]	16 (12.9)	14 (11.3)[a]
Hematuria and proteinuria	3 (2.7)	3 (2.7)[a]	31 (13.4)	31 (13.4)[a]	11 (8.9)	12 (9.7)[a]
Glucosuria	15 (11.7)	21 (16.4)[a]	6 (2.6)	9 (3.9)[a]	6 (4.7)	10 (7.8)[a]
Renal function indexes						
BUN (mM)	3.86 (2.75–4.81)	3.66 (2.50–4.70)[a]	5.09 (4.07–6.77)	5.03 (4.07–6.70)[a]	4.79 (3.64–5.62)	4.61 (3.61–5.81)[a]
SCr (μM)	34.00 (25.20–50.25)	43.00 (30.00–58.00)[b]	60.00 (48.00–75.00)	63.00 (49.00–79.85)[a]	54.00 (44.00–77.00)	56.44 (47.00–70.00)[a]
UA (μM)	280.50 (220.75–348.50)	290.00 (2334.50–354.00)[a]	207.00 (156.00–279.00)	216.00 (168.00–280.00)[a]	241.00 (193.25–298.75)	236.50 (185.75–290.25)[a]
CYS-C (mg/l)	0.90 (0.84–1.00)	0.90 (0.83–0.99)[c]	1.07 (0.96–1.27)	1.10 (0.96–1.29)[c]	1.025 (0.92–1.19)	1.03 (0.91–1.18)[c]
β2-MG (mg/l)	1.52 (1.33–1.69)	1.52 (1.37–1.72)[a]	1.90 (1.59–2.26)	1.96 (1.64–2.37)[a]	1.79 (1.53–2.02)	1.76 (1.52–2.05)[a]
RBP (mg/l)	34.00 (27.00–43.00)	34.40 (28.70–44.25)[a]	30.00 (24.25–36.00)	30.00 (24.00–36.00)[a]	32.50 (26.00–39.25)	32.00 (26.00–47.00)[a]
Urine composition						
Occult blood, positive (%)	9 (7.8)	6 (5.2)[a]	75 (32.5)	59 (25.6)[c]	29 (23.4)	24 (19.4)[a]
Protein, positive (%)	28 (24.8)	35 (31.0)[a]	105 (45.5)	111 (48.1)[a]	44 (35.5)	51 (41.2)[a]
Glucose, positive (%)	15 (11.7)	21 (16.4)[a]	15 (6.4)	13 (5.6)[a]	6 (4.7)	10 (7.8)[a]
Urobilinogen, positive (%)	44 (30.8)	47 (32.9)[a]	47 (20.2)	63 (27.1)[a]	33 (24.8)	32 (24.1)[a]
WBC	3 (1–11)	4 (2–13)[a]	11.5 (4–24)	10 (4–29)[a]	10 (3.5–19)	12 (4–30)[a]
RBC	2 (0–4)	2 (1–7)[a]	7 (2–16)	9 (3–18.5)[a]	5.5 (2–9.5)	6 (2–13)[a]
Squamous epithelial cell	0 (0–2)	0 (0–2)[a]	3 (0–12)	2 (0–12)[a]	4 (1–17.5)	5 (0–23)[a]
Mucous strands	10 (4–52)	8.5 (2–30)[a]	30 (3–133)	23 (2–88.5)[a]	41.5 (9.5–92.5)	25 (6–75)[a]
Nonsquamous epithelial cell	0 (0–0)	0 (0–1)[a]	0 (0–2)	0 (0–2)[a]	0 (0–1)	0 (0–1)[a]

BUN, blood urea nitrogen; CYS-C serum cystatin C; DMSA, dimercaptosuccinic acid; DPA, D-penicillamine; IQR, interquartile range; K-F, Kayser–Fleischer; RBC, red blood cell; RBP, retinol-binding protein; SCr, serum creatinine; UA, uric acid; WBC, white blood cell; β2-MG beta-2 microglobulin.
[a]$P > 0.05$.
[b]$P < 0.01$.
[c]$P < 0.05$.
Values are presented as median with IQR. *P* values when comparing before and after drug usage.

The dimercaptosuccinic acid group showed a significant reduction in urinary occult blood incidence (32.5%–25.6%, $P = 0.033$), whereas changes in leukocyte and red blood cell counts, proteinuria, and glucosuria were not significant. Copper chelators and zinc agents demonstrated limited effects on renal function markers in patients with WD, with the exception of the improvement in SCr levels in the zinc group and the reduction in cystatin C levels across treatments.

Estimated Glomerular Filtration Rate Trajectory

The estimated glomerular filtration rate ranged from 41.5 to 210.2 ml/min per 1.73 m^2 (median: 124.0; interquartile range: 104.0–137.4). Disease duration spanned 0.1 to 44.1 years (median: 7.9; interquartile range: 3.3–13.6). The estimated glomerular filtration rate negatively correlated with age ($R^2 = 0.16$, $P < 2.2 \times 10^{-16}$) and disease duration ($R^2 = 0.0092$, $P = 2 \times 10^{-5}$) (Figure 1a). It had weaker but significant negative correlation between estimated glomerular filtration rate and disease duration ($R^2 = 0.0092$, $P = 2 \times 10^{-5}$) (Figure 1b). Renal function stages varied by age as follows: 87.5% of patients aged 1 to 18 years were in stage 1 and 12.5% in stage 2 (Figure 1c and Supplementary Table S3). The proportion of stage 1 patients decreased with age, from 73.0% in patients aged 19 to 30 years to 42.9% in those aged > 50 years. More advanced stages (e.g., stage 3a and b) appeared predominantly in older age groups. Across all groups, the majority of patients were in stage 1, with proportions ranging from 70.7% (aged 6–12 years) to 80.9% (aged >12 years). Stage 2 was consistently present, whereas stage 3a and 3b appeared less frequently, primarily in longer disease duration (Figure 1d and Supplementary Table S4).

DISCUSSION

In patients with WD, copper accumulates not only in the liver and brain but also in various other organs, with renal copper content being one of the highest after the liver.[8] Liver injury can also be the cause of secondary impairment of other tissues. Few patients present with renal impairment as the initial symptom, which might lead to a misdiagnosis.

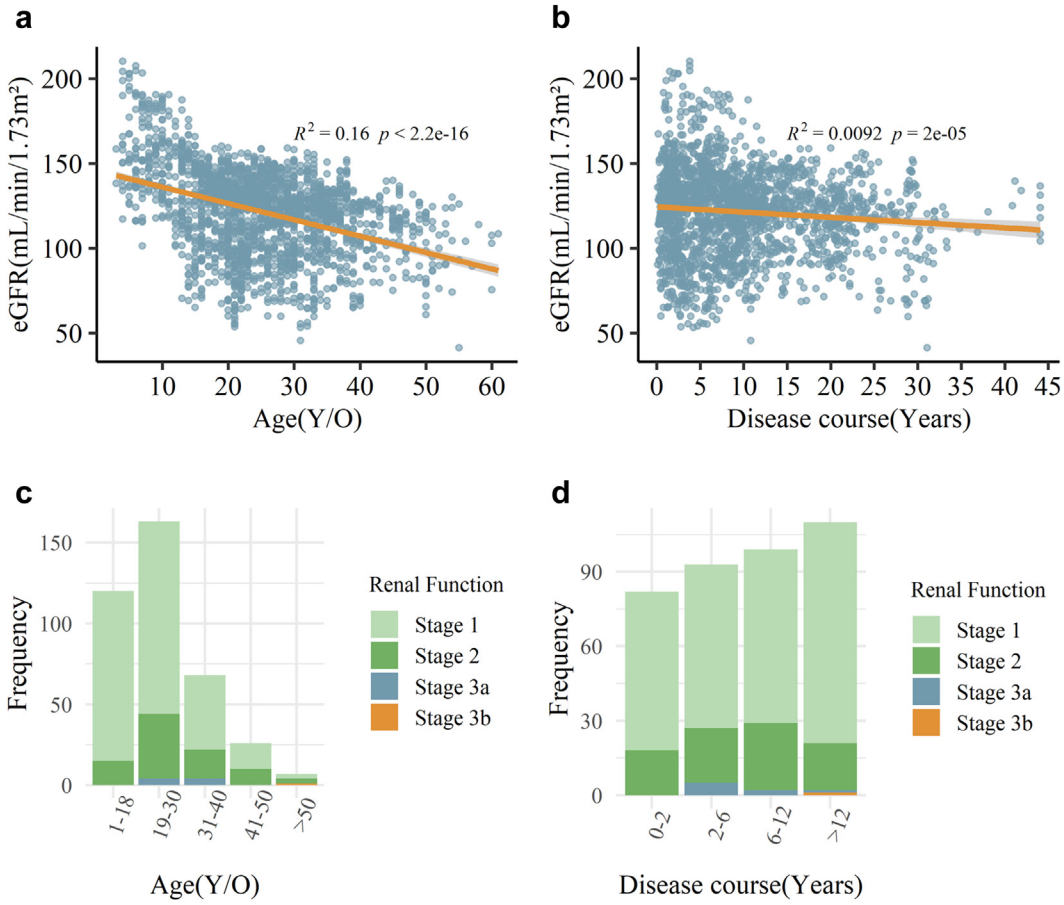

Figure 1. (a) eGFR shows a significant negative correlation with age ($R^2 = 0.16$, $P < 2.2 \times 10^{-16}$). (b) eGFR exhibits a weaker negative correlation with disease course ($R^2 = 0.0092$, $P = 2 \times 10^{-5}$). (c) Distribution of renal function stages across age groups. (d) Distribution of renal function stages across disease course groups. eGFR, estimated glomerular filtration rate.

Our findings revealed significant differences in urinary parameters and renal indicators between patients with WD and age-matched controls, indicating renal structural and functional damage even when it is not the first symptom. This impairment, seen in both pediatric and adult groups, suggests chronic, compensated progression of renal injury. Copper accumulation occurs in the renal tubules, causing glucosuria, proteinuria, hematuria, elevated beta-2 microglobulin, retinol-binding protein, and renal tubular acidosis. Thickened basement membranes impair tubular reabsorption. Hematuria with atypical red blood cells, significant proteinuria, and elevated blood urea nitrogen, SCr, and cystatin C suggest glomerular involvement.

Copper-chelation therapies did not critically affect renal function in the short term. Variations in proteinuria and glucosuria were observed, but major renal indicators remained stable. D-penicillamine may cause adverse effects such as proteinuria, hematuria, and lupus-like reactions. Proteinuria, linked to immune-mediated glomerulonephritis, occurs in 4% to 33% of D-penicillamine–treated patients, usually after 1 year.[9] Hematuria can develop within 3 months. Temporary dose adjustments are effective for managing these side effects. Limited data exist on dimercaptosuccinic acid renal impact, though cases of membranous nephropathy and urinary changes suggest its potential renal effects. Zinc therapy, a first-line maintenance treatment for asymptomatic and successfully treated patients with WD, has minimal adverse effects. Although zinc does not critically impact renal function, changes in SCr levels are noted, particularly in pediatric patients due to age-related physiological factors. Glomerular filtration stabilizes by age 1.5 to 2 years; however, SCr increases with increasing muscle mass, particularly during adolescence. Zinc therapy is associated with reduced SCr, potentially indicating improved renal function or reduced renal load. Elevated uric acid levels may signal early renal involvement even before significant liver or neurologic symptoms.

The estimated glomerular filtration rate negatively correlated with age, indicating progressive renal decline in patients with WD because of age-related kidney changes and WD-specific factors, such as copper toxicity and chronic liver disease. The weaker correlation with disease duration suggests that age

plays a more significant role than disease course in renal function decline, reflecting variability in WD progression and treatment. Renal function stages varied significantly by age. Stage 1 predominated in those aged 1 to 18 years but declined with age, whereas advanced stages (e.g., stage 3b) were more common in those aged > 50 years. Younger patients showed better renal function, likely due to earlier diagnosis and treatment. No significant differences were observed by disease duration. Most patients remained in stage 1, highlighting effective therapy. Advanced stages (3a and b) appeared in longer duration, emphasizing the need for long-term renal monitoring.

In conclusion, patients with WD often present with urinary abnormalities and renal impairment. Copper-chelation therapies and zinc, when appropriately managed, do not significantly worsen renal function in the short term. Clinicians should consider WD in the differential diagnosis of patients presenting with unexplained renal damage. A low-copper diet and proper medication are vital to prevent further damage. Regular monitoring is essential to detect early progression, and larger studies are needed to clarify age-related effects and treatment impacts on renal function.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Z-WZ contributed to data curation, formal analysis, and writing the original draft. M-HX contributed to data curation and formal analysis. L-NF contributed to data curation and formal analysis. R-MW contributed to data curation. W-QX contributed to writing-editing. G-MY contributed to data curation. YD contributed to conceptualization and project administration. Z-YW contributed to supervision, conceptualization, project administration, writing-review and editing.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary Reference.

Figure S1. Criteria and flowchart for selecting study subjects and follow-up data.

Table S1. The baseline clinical parameters of patients with Wilson's disease and controls.

Table S2. Laboratory parameters among different phenotypes of patients with Wilson's disease.

Table S3. The distribution of renal function stages by age groups.

Table S4. The distribution of renal function stages by disease course groups.

REFERENCES

1. Członkowska A, Litwin T, Dusek P, et al. Wilson disease. *Nat Rev Dis Primers*. 2018;4:21. https://doi.org/10.1038/s41572-018-0018-3
2. Wu ZY. Chinese guidelines for diagnosis and treatment of Wilson's disease 2021. *Chin J Neurol*. 2021;54:310–319.
3. European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol*. 2012;56:671–685. https://doi.org/10.1016/j.jhep.2011.11.007
4. Wang H, Zhou Z, Hu J, et al. Renal impairment in different phenotypes of Wilson disease. *Neurol Sci*. 2015;36:2111–2115. https://doi.org/10.1007/s10072-015-2322-y
5. Dong Y, Wu ZY. Challenges and suggestions for precise diagnosis and treatment of Wilson's disease. *World J Pediatr*. 2021;17:561–565. https://doi.org/10.1007/s12519-021-00475-4
6. Dzieżyc-Jaworska K, Litwin T, Członkowska A. Clinical manifestations of Wilson disease in organs other than the liver and brain. *Ann Transl Med*. 2019;7(suppl 2):S62. https://doi.org/10.21037/atm.2019.03.30
7. Dang J, Chevalier K, Letavernier E, et al. Kidney involvement in Wilson's disease: a review of the literature. *Clin Kidney J*. 2024;17:sfae058. https://doi.org/10.1093/ckj/sfae058
8. Li X, Hu F, Xu G. Membranous nephropathy caused by dimercaptosuccinic acid in a patient with Wilson's disease: a case report and literature review. *BMC Nephrol*. 2023;24:147. https://doi.org/10.1186/s12882-023-03201-6
9. Kumar S, Patra BR, Irtaza M, et al. Adverse events with d-penicillamine therapy in hepatic Wilson's disease: a single-center retrospective audit. *Clin Drug Investig*. 2022;42:177–184. https://doi.org/10.1007/s40261-022-01117