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CKJ REVIEW

# Kidney involvement in Wilson's disease: a review of the literature

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## ABSTRACT

Wilson's disease (WD) is a rare inherited disease due to the mutation of the ATP7B gene, resulting in impaired hepatic copper excretion and its pathological accumulation in various organs such as the liver, the nervous system, or the kidneys. Whereas liver failure and neuropsychiatric disorders are the most common features, less is known about the renal complications. We conducted a review of the literature to define the characteristics and pathophysiology of kidney involvement during WD. This review shed light on strong evidence for direct copper toxicity to renal tubular cells. Excessive tubular copper accumulation might present with various degrees of tubular dysfunction, ranging from mild hydroelectrolytic and acid–base disorders to complete Fanconi syndrome. Proximal and distal renal tubular acidosis also favors development of nephrolithiasis, nephrocalcinosis, and bone metabolism abnormalities. Indirect complications might involve renal hypoperfusion as occurs in hepatorenal or cardiorenal syndrome, but also tubular casts' formation during acute hemolysis, rhabdomyolysis, or bile cast nephropathy. Acute kidney failure is not uncommon in severe WD patients, and independently increases mortality. Finally, specific and long-term therapy by D-penicillamin, one of the most efficient drugs in WD, can cause glomerular injuries, such as membranous nephropathy, minimal-change disease, and, rarely, severe glomerulonephritis. Altogether, our study supports the need for interdisciplinary evaluation of WD patients involving nephrologists, with regular monitoring of tubular and glomerular functions, to provide adequate prevention of renal and bone involvement.

**Keywords:** Fanconi syndrome, hypercalciuria, nephrolithiasis, renal acidosis, Wilson's disease

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## INTRODUCTION

Wilson's disease (WD) is a rare inherited disorder that is due to bi-allelic mutations in *ATP7B*, the gene encoding transmembrane copper-transporting ATPase2 (ATP7B). This results in a defect of copper excretion into the bile, and its secondary accumulation in the liver and various tissues, such as the brain, the eyes, the heart, or the kidneys [1]. In a meta-analysis including studies from various European and Asian countries, the genetic prevalence of WD is estimated at 12.7/100 000 individuals, but is highly heterogeneous, with a much higher prevalence in isolated populations or Eastern Asian countries, and affecting between 1000 and 1500 patients in France [2–4]. Increasing awareness among physicians and prompt diagnosis are of importance, since early and lifelong treatment using copper chelators (D-penicillamine, trientine salts) or zinc salts could efficiently prevent cirrhosis, brain injury, and death [5]. Whereas hepatic failure, neurodegenerative or psychiatric disorders are the most common manifestations in the natural course of WD and have been well studied, less is known about the renal involvement.

Acute kidney failure during hepatorenal syndrome (HRS) in the end-stage of WD-related cirrhosis is a life-threatening consequence well-known by clinicians. Other renal features have, however, been mostly overlooked. Indirect complications, such as bile cast nephropathy, rhabdomyolysis, or massive acute hemolysis in the most severe cases, can also lead to acute kidney injury. Excessive non-ceruloplasmin-bound copper levels lead to increased urinary copper excretion, which is believed to induce direct toxicity to the tubular cells. Therefore, various tubular dysfunctions, responsible for hydroelectrolytic imbalance, acid–base disorders, or nephrolithiasis, have been described in WD. However, expert guidelines rarely recommend tubular function screening and dietary education [6]. Besides, long-term treatment with D-penicillamine (DPA) is known to induce glomerular diseases, such as membranous nephropathy, which called for new and safer drugs. In this review, we conducted a systematic analysis of the literature to describe copper metabolism and toxicity within the kidneys, to sum-up the different kidney involvements during WD and better define their pathophysiology, and tried to provide practical recommendations for adequate monitoring and prevention for these patients.

## MATERIALS AND METHODS

A systematic literature review was performed to identify studies regarding kidney involvement during WD on PubMed. The literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (http://www.prisma-statement.org). The following terms (Title/Abstract), without any search filters, were used: (Wilson disease OR Wilson's disease) AND (renal OR kidney OR nephropathy OR Fanconi OR tubulopathy OR nephrolithiasis OR glomerulonephritis OR proteinuria OR nephrotic) NOT diabetes (to exclude studies mentioning Kimmelstiel–Wilson nodules in diabetic nephropathy). Articles regarding both adult and pediatric WD patients were included. The relevant articles were selected based on the titles and the abstracts. Articles unrelated to WD and/or kidney involvement were excluded. This review was based on full-text articles only.

## RESULTS

A total of 397 research publications were identified on PubMed. Of these, 278 articles were excluded, either because they were not about WD ($n = 83$), not about kidney involvement during WD ($n = 144$), because there was no full text available ($n = 49$), or because of duplicate ($n = 2$). Finally, 119 articles, including 24 observational studies and 75 case reports, were included in this review (Fig. 1).

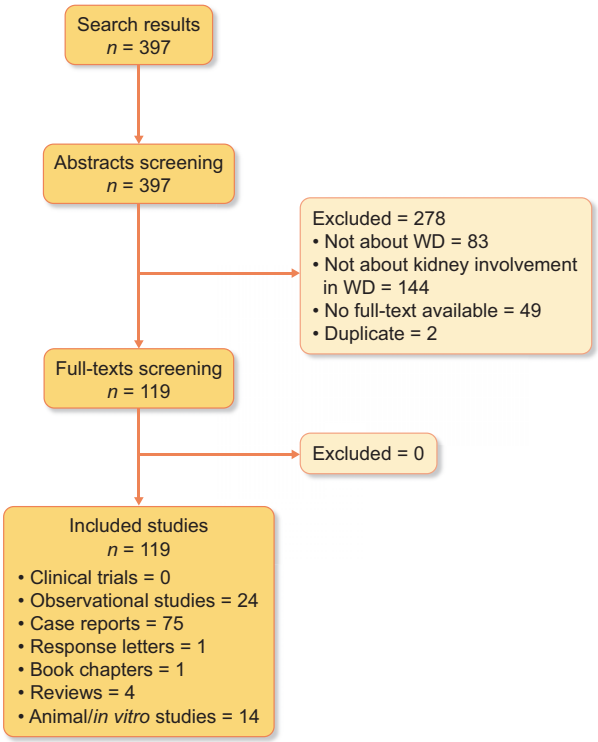


**Figure 1:** Flow-chart of the literature review.

### Copper metabolism in kidneys

Copper plays an essential role in mammalian physiology, as it acts as a cofactor for many key metabolic enzymes such as those involved in cell respiration or free radical defense pathways [1]. Conversely, excess copper is toxic to most living cells, and maintenance of body copper balance is thus critical. Renal copper content is among the highest in the body after the liver [7]. Promptly after intraperitoneal injection of copper-albumin complexes in mice, notable elevations of copper content were observed in the kidneys, persisting >6 hours, in concentrations 3–6 times higher than normal values (4–5 µg/100 mg wet tissue, which is similar to the amounts reached in the liver), before decreasing after 48 hours [8]. Staining with rubeanic-acid revealed copper accumulation in the glomerular tufts and subcapsular spaces as well as in the content of tubules, 6 hours after the injection. At 24 hours, more marked staining was found in the tubular cells, with granules irregularly distributed throughout the cytoplasm. In a mouse WD model and two WD patients, total body scans using radioactive copper also revealed progressive and unusual heavy concentration of the isotope in the liver, then the kidneys, compared to control littermates and two healthy individuals [9, 10]. Thus, excess serum copper might possibly lead to its increased glomerular filtration and tubular reabsorption.

Kidneys regulate their copper content more effectively than many other organs in case of copper deficiency or excess. Two copper-transporting ATPases, ATP7A and ATP7B, contribute to

this homeostasis through regulation of copper trafficking between the different cellular compartments [1, 11]. In adult mice, ATP7A is expressed throughout the kidney but is mostly located in cytoplasmic vesicles of tubular cells. Acute elevation of serum copper, via intraperitoneal injection, results in the redistribution of ATP7A toward the basolateral membrane, which is believed to allow copper excretion and protect renal cells against overload. ATP7B is also thought to be required for renal copper homeostasis, as ATP7B-deficient (*Atp7b*$^{-/-}$) mice, a murine model of WD, showed accumulation of metallothionein-bound copper in the tubular cells [11–13]. However, renal copper in this model was just slightly increased, suggesting a compensatory export by ATP7A [11]. Conversely, during Menkes disease, caused by inactivating mutations of the ATP7A transporter, copper accumulates considerably in the proximal tubular cells. This suggests that human renal ATP7B alone is not sufficient to protect renal cells from copper overload [11, 14]. This is likely due to a kidney-specific regulation of the ATP7B transporter, which, unlike ATP7A or hepatic ATP7B, does not traffic from the Golgi network toward the plasma membrane to export copper. This difference might result from an inefficient translation of the exon 1 of renal ATP7B [14]. Thus, renal ATP7B might have a less important role in copper export than ATP7A or hepatic ATP7B. Nevertheless, very high copper content has been constantly detected in the kidneys of WD patients. In eight untreated patients, the copper concentration in the kidneys at autopsy was significantly more important compared to a control group (904 vs. 15 $\mu$g/g dry tissue) [15]. This suggests that both ATP7A and ATP7B are required to counterbalance excess renal copper in humans [15].

## Copper toxicity to kidney cells

It was already suggested in the early 1950s that copper deposition in the kidneys could have toxic properties, although the mechanisms had not yet been defined precisely at that time [16]. Indeed, copper poisoning leads to fatal renal failure, mostly caused by acute tubular necrosis, as occurs in acute liver failure and fulminant forms of WD [17–19]. Likewise, a large cross-sectional study in China among 3285 individuals were able to link chronic copper exposure to a higher incidence of chronic kidney disease, with a positive linear dose-dependent association with the levels of cupremia [20]. This phenomenon has also been observed in chronic poisoning with other metals, such as lead, mercury, or cadmium [21]. There is in fact much evidence in animal studies supporting the renal toxicity of copper. Whether in goldfish kept in ionized copper-enriched water, or in mice receiving intraperitoneal injections of copper-albumin complexes, studies have consistently shown early cytologic alterations in the epithelium of renal tubules, such as cell vacuolation or swelling, pyknosis, or karyorrhexis of the nuclei, and sometimes marked proximal tubular necrosis. In any case, concentrations of copper in the kidneys equaled those occurring naturally in WD patients [8, 22]. Mice usually died 24–48 hours after the injection; those who survived showed various degrees of epithelial regeneration, with mitotic activity and hyperplasia, along with parenchyma calcification. The glomeruli and bloods vessels were, however, unaltered, highlighting the tubular tropism of copper toxicity [8]. After demonstrating kidney lesions in chronically copper-poisoned rats in the 1960s, Wolff reported a series of post-mortem kidney specimens of 5 WD patients [23, 24]. In all patients, kidney sections revealed focal areas of tubular injury and atrophy, without glomerular abnormalities. Rubeanic-acid staining demonstrated constant intracytoplasmic granular deposition of copper in the proximal and distal tubular cells. The fact that the most dramatic morphological alterations occurred in the same areas of heavy copper deposition suggested a cause-and-effect relationship [24]. This renal toxicity might be in part due to oxidative stress. By administrating copper-sulfate to Wistar rats, Kumar *et al.* showed marked decrease in glutathione and total antioxidant capacity in liver and kidneys, which were inversely correlated with the levels of serum transaminases, bilirubin, and blood urea nitrogen, suggestive of kidney failure [25]. Copper-metallothionein complexes, released on hepatocellular necrosis into circulation, have also been suspected to induce direct lesions into tubular cells in Long-Evans Cinnamon (LEC) rats, a murine WD model [26]. Finally, copper might also trigger kidney fibrosis by lysyl oxidase-mediated matrix crosslinking [27]. Taken together, it is likely that copper itself is an important factor in the pathogenesis of renal abnormalities in WD.

## Proximal tubule

The tubular epithelial cells lining the distinct nephron segments are highly specialized, with transport functions accomplished by solute-specific channels. In the proximal tubule (PT), some major elements are nearly totally reabsorbed by active transepithelial pathway or passive diffusion: glucose, phosphate, amino acids, uric acid, low molecular-weight proteins, and bicarbonate. These reabsorption activities require a large amount of energy provided by ATP production through the oxidative mitochondrial metabolism. Thus, PT cells are sensitive to stress and injuries, which can bring to abnormal transport functions, the so-called Fanconi syndrome (FS). Cooper *et al.* were among the first to suggest a partial FS in WD patients [28]. In fact, increased quantities of amino acids in the urine have been described by Uzman and Denny-Brown in 1948[17]. Screening of asymptomatic siblings had in some cases revealed abnormal aminoaciduria before the occurrence of any other clinical manifestations [29]. It was initially suggested that this aminoaciduria might represent either a failure of deamination of amino acids by an impaired liver, or an underlying defect in the metabolism of amino acids resulting in an excessive excretion by a normal kidney [16]. In his series of six non-treated patients, Cooper found a 2–3-fold increase of amino acids urinary excretion in all cases, even in fasting state, independent of the protein content of the diet or the urine volume, as compared to healthy individuals or patients with chronic liver failure of other causes. Rapid infusion of amino acids did not lead to abnormal rise in their plasma concentration or slower decrease to normal values, excluding a failure in cellular absorption or deamination. Because the 10 essential amino acids tested in this study were all increased in the urine samples, any specific metabolic defect, such as occurs in cystinuria for example, can also be excluded. Moreover, renal glycosuria was also observed in half of the patients. Additionally, WD patients frequently exhibit hypouricemia [30, 31]. Significant low-weight proteinuria was also noted in 25% of 40 patients in Sözeri's report, mostly in patients with no or short duration of treatment [32]. In another small series of nine patients without significant liver dysfunction, Bearn *et al.* measured glomerular filtration rate (GFR) by inulin clearance, and assessed tubular functions [33]. As expected, most of patients exhibited decreased GFR (49–107 ml/min), and the degree of renal impairment paralleled the severity and duration of overt disease, suggesting a progressive deterioration of renal function. Excessive clearance of amino acids and uric acid was again constantly observed. Six patients had a reduced phosphate reabsorption capacity, and in five of them, the serum

phosphate was either decreased or in the low normal range. Although spontaneous glycosuria was not usually present in this series, the maximal tubular capacity to reabsorb glucose was reduced in varying degrees in all tested patients. Last, they tended to have alkaline urine (pH 6.6–8). In two tested patients, after ingestion of ammonium chloride, there was a significant decline in urine pH and increase in titratable acidity, along with disappearance of bicarbonate, suggesting the absence of urinary acidification defect. These findings suggest impairment in PT reabsorption of bicarbonate, responsible for a type II renal tubular acidosis (RTA). In very few case reports, renal biopsy was performed in WD patients presenting with FS, and found either marked alterations of mitochondria mainly within injured PT cells, or numerous electron-dense bodies in the subapical areas of the cytoplasm of renal tubules, possibly suggestive of metalloproteins according to the authors [34, 35]. Taken together, one might conclude that WD can be responsible for a complete PT dysfunction. Most importantly, several authors reported the beneficial effects of copper chelators in normalizing aminoaciduria, low-weight proteinuria, and improving serum uric acid concentration within months and up to 2 years [31, 32, 35–39]. Most studies included only 10–20 patients. Another study showed correction of proteinuria and phosphate clearance in nine patients who underwent orthotopic liver transplantation for WD, compared to nine transplanted for other causes. This argued for a renal toxicity of copper accumulation, rather than a primary renal defect [40].

## Distal tubule

The distal tubule (DT) is involved in adjusting blood pressure by regulating sodium reabsorption under the control of the renin-angiotensin-aldosterone system (RAAS). Sodium reabsorption is coupled with the excretion of equivalent number of cations, mainly represented by potassium and protons, through specific channels. DT also contributes to the acid–base balance, by excreting $H^+$ ions. DT dysfunction might therefore result in type I RTA, revealed by metabolic acidosis with urinary acidification defect, characterized by the inability to decrease urine pH after an acid load. Walshe *et al*. investigated the kidney acidification capacity in 20 patients, of whom 10 had received little or no treatment at the time of the study [41]. Contrary to the findings of Bearn *et al*. who found in two patients signs of proximal type II RTA, these authors found that eight of the naive patients could not decrease their urine pH below 6.22 and form ammonia after an ammonium chloride load. Conversely, all the treated patients had a normal acidification capacity. Strikingly, the naive patients improved their acidification capacity after 1 year of treatment, with a minimum pH urine down to 5.22.

Potassium handling in renal tubules is complex, with up to 70% of filtered potassium reabsorbed through the PT, and only 10–20% in the DT. On RAAS activation, triggered by hypovolemia, which can be possibly induced in WD patients by salt wasting in the PT, Henle loop, or DT, excretion of potassium in DT can markedly increase over the filtered quantities. A distal defect in proton excretion, leads to preferential excretion of potassium into urine. Thus, renal potassium wasting during WD might result from both PT and DT defects. Profound hypokalemia is a life-threatening electrolyte disorder from tubular dysfunction, as it might cause both cardiac arrythmia and muscular paralysis. Several case reports highlighted this rare complication, mostly in WD children. An 11-year-old girl, presented with brutal paraplegia and acute respiratory failure within 1 day. Investigations revealed an unsuspected WD, with little liver and neurological involvement, associated glycosuria and aminoaciduria, along with polyuria and dehydration, all attributed to a WD-specific tubular dysfunction, resulting in refractory hypotension, acute kidney failure, and ultimately death [42]. Another 13-year-old boy presented with recurrent episodes of generalized proximal muscle weakness due to hypokalemia, causing multiple hospitalizations for potassium-chloride perfusions. Only 5 years after, because of the occurrence of flapping-like tremor of the upper limb, he was diagnosed with WD. At the same time, he developed a type II RTA, associated with partial FS. In another report, a 17-year-old boy with WD also presented with recurrent hypokalemic muscle weakness for 5 years. In this case, defect in potassium reabsorption was confirmed by an abnormally high transtubular potassium gradient, and this was attributed to a type I distal RTA. In these two cases, hypokalemia disappeared after DPA initiation [43, 44]. Several other similar case reports have been published [45, 46].

## Nephrolithiasis, nephrocalcinosis, and bone metabolism

Nephrolithiasis is a common disease, affecting 5–10% of the general population. Hypercalciuria is the most frequent predisposing factor found in half of cases, and is mostly caused by dietary habits and rarely by monogenic or metabolic disorders. FS results in hypercalciuria and hyperphosphaturia, leading to the formation of calcium-phosphate or calcium-oxalate renal stones. Renal losses of phosphate are frequently associated with an increased hydroxylation of 25-hydroxy-vitamin D into calcitriol, thus increasing digestive absorption of calcium and phosphate, and maintaining this vicious cycle. Furthermore, metabolic acidosis, caused either by proximal or distal RTA, induces bone demineralization and leakage of calcium and phosphate, which ultimately accumulate into the tubules. Systemic acidosis could also increase tubular absorption of citrate, a potent natural crystal inhibitor, and hypocitraturia consequently favors stone formation. Defect in renal acidification is also responsible for alkaline pH, thus favoring tubular crystallization of calcium-phosphate. Altogether, tubular dysfunction during WD might lead to nephrolithiasis, nephrocalcinosis, and ultimately kidney failure, but also to various degrees of bone abnormalities and fractures [47–49]. This trend to hypercalciuria has been long stated by Litin *et al*. in the 1950s, who reported six patients: four with hypercalciuria and two who also presented with nephrocalcinosis and nephrolithiasis [50]. WD has been rarely diagnosed solely in front of atypical nephrolithiasis, both in pediatric and adult case reports [51–54]. Hypercalciuria has been reported as a very early manifestation of WD. One of the reported patients had hypercalciuria and nephrolithiasis at 5 years of age as the first and only sign of WD for the subsequent 10 years [55]. Constant associated tubular dysfunction argued for a WD-specific disorder. Fulop *et al*. described distal RTA in 4 out of 12 patients, one of them having medullary nephrocalcinosis [56]. Strikingly, Wiebers *et al*. found that up to 16% of their series of 45 patients had a history of renal stones, which seemed to be significantly more frequent than in the general population [57]. In four of their seven patients with nephrolithiasis, renal stones were symptomatic and discovered at the time or before the diagnosis of WD. In this small group of stone formers, 3/7 (43%) had hypercalciuria, and 4/5 (80%) had partial RTA. Contrary to the other tubular disorders, there is not much evidence in the literature of calcinuria normalization after initiation of WD treatment.

## Acute kidney failure

Acute kidney failure (AKF) occurs by renal lesions [acute kidney injury (AKI)] and/or by poor perfusion of nephrons, without direct damage to the kidney parenchyma (prerenal syndrome). In a large survey in the USA among 9046 hospitalizations in WD patients, AKF was diagnosed in 197 of them (2.14%), and was independently associated with a higher risk of mortality [OR 4.09, 95%CI (2.19–7.65)] [58].

Clinicians are familiar with HRS in severe hepatic forms of WD. Pathophysiology of HRS during cirrhosis, whatever the cause, are already nicely reviewed by Ginès *et al.* [59]. HRS involves complex disturbances in circulatory function, due to a marked portal hypertension and splanchnic arterial vasodilatation, which trigger the release of systemic vasoconstrictor factors, including RAAS and sympathetic nervous system, leading to renal vasoconstriction, and is thus responsible for hypoperfusion and AKF. Other major factors of HRS are a systemic inflammatory reaction characteristic of advanced cirrhotic patients, or bacterial translocation from spontaneous peritonitis, which can bring to acute tubular necrosis. Medical therapy consists of vasoconstrictor drugs to counter splanchnic vasodilatation together with albumin perfusion for volume expansion. Prognosis of HRS is poor without liver transplantation, with a median survival of $<$3 months.

AKF during cardiorenal syndrome involves hemodynamic (low cardiac output, fluid retention, decreased renal perfusion, vasoconstriction), hormonal (RAAS and sympathetic system activation), and inflammatory factors (IL6, TNF$\alpha$, free radicals), along with underlying predisposing factors (atherosclerosis, cirrhosis), and has already been reviewed [60]. Treatment is based on adequate fluid depletion using association of diuretics, and specific therapy for underlying heart conditions. Cardiac manifestations in WD have been reviewed recently by Chevalier *et al.*, and include cardiomyopathy (mainly left ventricular hypertrophy, diastolic, and, less frequently, systolic dysfunction), arrhythmia, conduction abnormalities, and dysautonomia [61]. Mechanisms might also involve direct toxicity of copper to the cardiomyocytes and release of free oxygen radicals. In a study of 463 WD patients, a high incidence of atrial fibrillation (29%) and congestive heart failure (55%) were observed [62].

Direct copper-induced tubular injury is not the only factor of AKI in the natural course of WD. In fact, indirect tubular injuries, triggered by bile casts, rhabdomyolysis, or acute hemolysis, can also be involved.

Bile cast nephropathy (BCN) is usually seen in patients with severe hyperbilirubinemia due to a wide range of hepatobiliary system diseases. This is caused by precipitation and local toxic effects of bile acids into the renal tubules. Renal biopsy reveals acute tubular injury with green-brown pigment within tubular epithelial cells, and red pigmented granular casts. Hall's stain for bile turns these casts green. Biopsy-proven BCN has exceptionally been reported in the course of fulminant hepatic WD [63].

Rhabdomyolysis is usually an indirect complication during WD, favored by severe renal hypokalemia and hypovolemia. Direct toxicity of copper into muscles has also been proposed by Propst *et al.*, who reported the case of a 17-year-old man presenting with recurrent mild rhabdomyolysis and AKI. In this patient, potassium levels were not provided, but copper content in muscle tissues was indeed high as compared to normal values. Trientine drug-induced rhabdomyolysis has also been suspected in some cases [64, 65]. Mechanisms of AKI during rhabdomyolysis are multiple, including tubular precipitation of myoglobin (released by injured muscles) casts, direct tubular toxicity of myoglobin, micro-circulation inflammation, and mostly hypovolemia caused by fluid sequestration within the injured muscular tissues. Hence, rare cases of rhabdomyolysis-induced AKI have been reported in WD [66, 67].

Acute hemolysis is a well-recognized manifestation of WD. It occurs due to excessive liberation of copper into the circulation during hepatocellular necrosis, with direct oxidative stress on red blood cells and damage to their plasma membranes. In some cases, hemolysis precedes a rapidly progressive course, ending with fulminant liver and renal failure. Hemolysis-induced AKI is multifactorial, and can be caused by tubular precipitation of hemoglobin casts, heme breakdown-products, and labile iron inducing mitochondrial damage, cytokine release, endothelial activation, and interstitial inflammation within the kidneys, causing tubular cell necrosis. Fatal cases of severe hemolysis responsible for anuric AKI have thus been described in WD [68, 69]. Hamlyn *et al.* for example reported the history of two girls, aged 12 and 17 years, requiring extrarenal purification, who unfortunately died within 48 hours [70]. Therapeutic management is limited in this context since copper chelators are less efficient in the absence of residual kidney function. Therefore, salvage therapies using extracorporeal copper-removal techniques are the only options: this includes peritoneal dialysis, hemodialysis, especially post-dilution continuous hemofiltration with high permeability membrane, albumin dialysis, or plasmapheresis, which allow optimal clearance of protein-bound copper [70–82]. In a few cases, these palliative techniques allowed normalization of serum copper levels and prolonged patients survival, and served as a bridge until orthotopic liver transplantation [71, 72, 75–78, 80–82].

## Glomerular diseases

Direct glomerular injury is uncommon during WD. Most of the rare observations were related to the decreased clearing capacity of the liver, leading to abnormal deposition of immune-complexes in the glomeruli, such as occurs in IgA nephropathy and membranoproliferative glomerulonephritis [83–90]. These complications usually respond to copper-chelator therapies.

Conversely, glomerular adverse effects of DPA are frequent and have been first reported in the early 1960s, in WD or other systemic diseases. Estimated incidence of glomerular proteinuria (PU) varies from 10% to 20% in the first year of treatment, of whom one-third would develop nephrotic syndrome (NS) [91]. The risk of PU seems to decrease significantly after the first year. FDA adverse event reporting system revealed that DPA use was associated with a 6–7-fold increased risk of renal impairment [92]. In a large study of 163 WD patients, Merle *et al.* estimated that 11% had nephrotoxicity under DPA [93]. The most common form of DPA-induced renal disorders is membranous nephropathy (MN) [94–97]. MN is caused by immune-complex deposition on the outer side of the glomerular basement membrane, resulting in NS, classically revealed by anasarca and kidney failure. The exact pathogenesis of MN in this condition is unclear, most authors believed that DPA triggers formation of immune-complexes involving antibodies targeting DPA [94]. However, studies failed to prove the presence of DPA as an antigen within the subepithelial deposits. Owing to its low molecular-weight, DPA regarded as a chemical substance is not immunogenic, but could act as a potent hapten, thus enhancing immunological presentation of other antigens involved in the pathogenesis

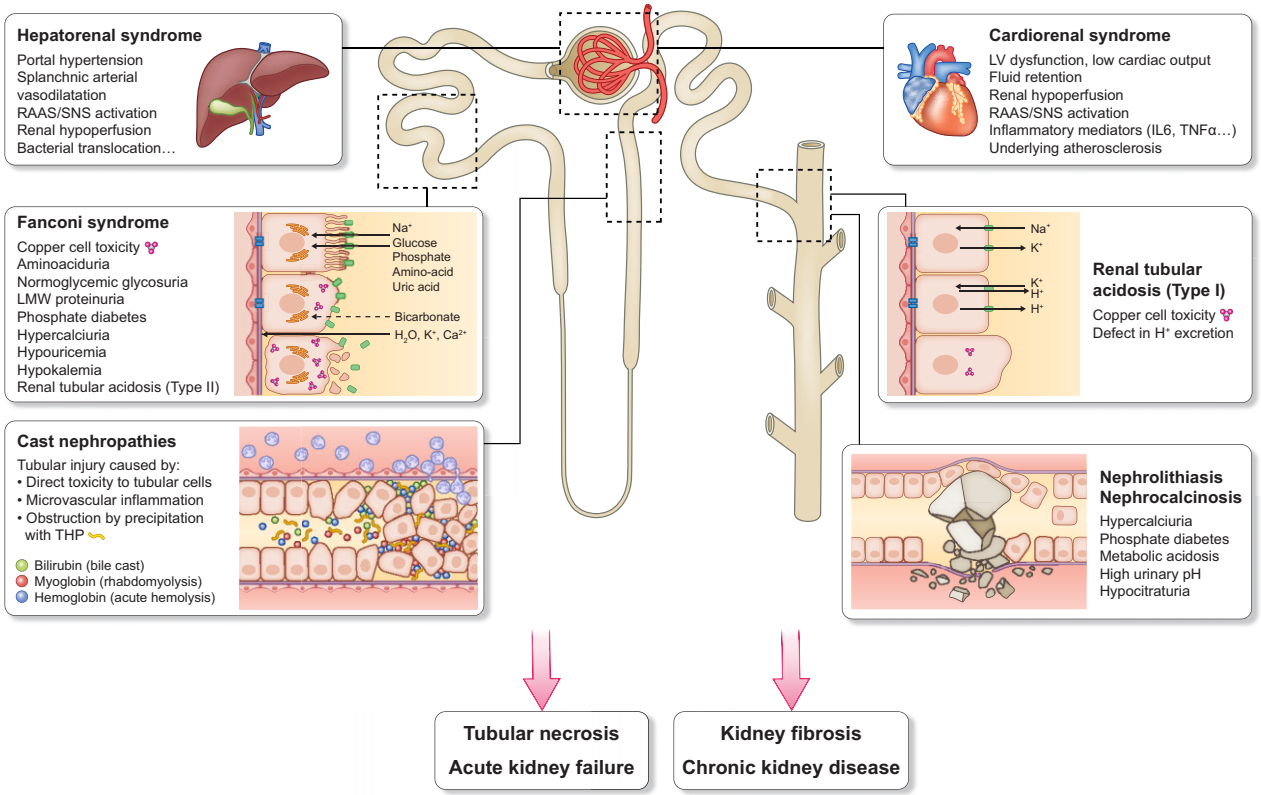


**Figure 2:** Overview of kidney involvements in WD. Mechanisms of renal impairment during WD involve: (i) prerenal syndrome mainly caused by liver and/or congestive heart failure responsible for renal hypoperfusion, (ii) AKI caused by direct copper toxicity to tubular cells or by cast nephropathies involving bilirubin, myoglobin or hemoglobin, and (iii) several tubular dysfunctions revealed by FS, RTA, and/or nephrolithiasis. Tubular injury might lead to AKF and subsequently chronic kidney fibrosis. Abbreviations: LMW, low molecular-weight protein; LV, left ventricular; SNS, sympathetic nervous system; THP, Tamm–Horsfall protein.

of MN. Delay between DPA initiation and first renal symptoms varied with a median time of 7 months (up to 5 years) [95, 96, 98–100]. Siafakas *et al.* reported however an early-onset of NS in a 12-year-old boy, 2 weeks after DPA initiation [101]. NS is usually resolved within months after DPA discontinuation, but can persist up to 2 years and rapidly reoccur once the treatment resumes [95, 96, 98, 99]. Some authors reported the efficacy of steroids (average dose of 0.5 mg/kg/day) on PU, while maintaining, but mostly not, DPA treatment [95, 96, 98–100].

Other glomerular diseases have been described as possible adverse effects of DPA. In a systematic review, Habib *et al.* included 63 patients presenting with PU under DPA, 73% treated for rheumatoid arthritis, 9% for WD, PU occurring after a mean duration of 7.6 months: 55% had a diagnosis of MN, and 27% had a NS without any significant glomerular abnormalities in kidney biopsy, thus diagnosed with minimal-change disease (MCD) [95]. Hall *et al.* studied 33 patients who developed PU under DPA for rheumatoid arthritis, and found 29 cases of biopsy-proven MN, and two cases of MCD [96]. In case reports of DPA-induced MN, authors also frequently reported associated patterns of proliferative glomerulonephritis, such as mesangial cell proliferation or endocapillary inflammation, whereas features of MN seemed focal or questionable, with few subepithelial deposits visible only by electronic microscopy [98]. Indeed, in the review of Habib *et al.*, 6% of the patients had focal mesangioproliferative or membranoproliferative glomerulonephritis, rather than a classical MN [95]. Drug-induced systemic lupus with glomerulonephritis, for example, has been described up to 8 years after DPA initiation, with complete resolution after withdrawal [35, 102, 103]. In more severe cases, crescentic glomerulonephritis with proliferation of parietal epithelial cells and necrosis of glomerular capillaries walls has been observed [104]. Sternlieb *et al.* reported three atypical cases of fulminant crescentic glomerulonephritis and fatal pulmonary hemorrhage in WD patients after 2–3 years of DPA treatment, which are similar to what is observed in Goodpasture syndrome or systemic ANCA vasculitis [105]. However, immunofluorescence study was available only in one case, and showed atypical granular IgG and complement deposits, primarily found in the mesangium. Also, there was no proof of circulating ANCA or antibodies targeting GBM. Bienaimé and others also reported three cases of pauci-immune glomerulonephritis, two of them associated with anti-myeloperoxidase ANCA in a 19-year-old woman and a 13-year-old girl after 2 and 5 years of DPA treatment for WD, respectively [106–108]. Because of the rarity of these severe glomerulonephritis among patients under DPA, the long delay after drug initiation, and systematic use of immunosuppressants combination in this context, it is not possible to make a clear cause-and-effect relationship. Fortunately, all these side effects seem specific to DPA use, and are not common in patients using trientine or zinc salts [99, 101, 109].

## DISCUSSION

Kidney involvement in WD has been mostly overlooked in current expert guidelines. This review of the literature has shed

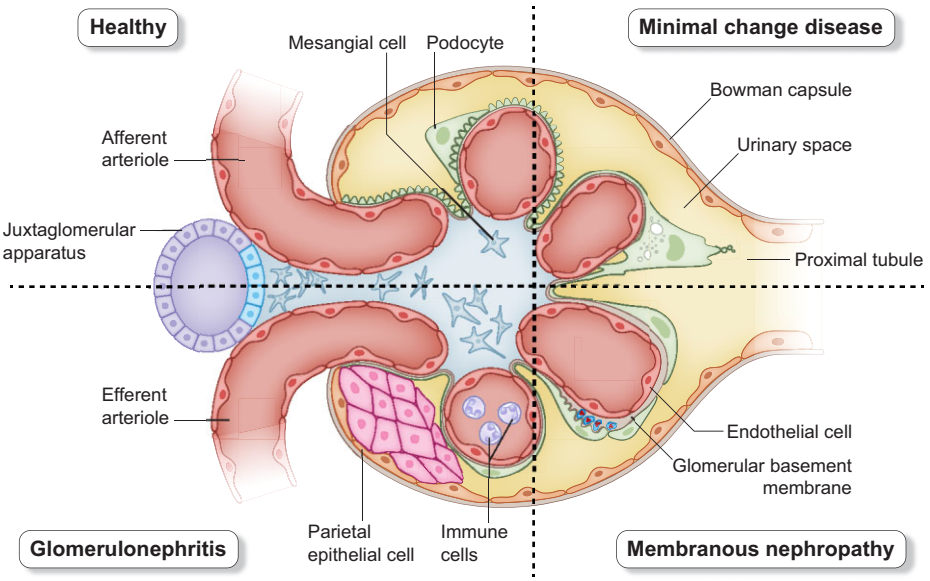


**Figure 3:** Overview of glomerular adverse effects of DPA treatment. DPA treatment, for WD or other systemic diseases, might cause: (i) MN, by abnormal deposition of immune-complexes of unknown nature in the outer layer of the glomerular basement membrane, (ii) MCD characterized by massive podocytes detachment in the urinary space and brutal NS, or (iii) glomerulonephritis with endocapillary, mesangial, and/or crescentic parietal proliferation, which can be responsible for severe kidney failure.

light on rich evidence for copper toxicity to renal tubular cells, and also numerous small observational studies highlighting tubular and glomerular disorders (summarized in Fig. 2). As is often the case in rare diseases, subtle renal manifestations might not be noticed. However, adequate monitoring is needed for the prevention of further complications, such as hydro-electrolytic and acid–base disorders, nephrolithiasis, or bone abnormalities.

The global prevalence of renal impairment in WD has been rarely addressed in cohort studies, without further details about the phenotypes, the causes or the consequences of a patient's treatments, and quality of life. Chronic kidney failure does not seem frequent in patients without severe hepatic dysfunction. In a cohort of 691 patients studied by Wang *et al*., serum creatinine levels rarely rose above 100 µmol/l [110]. Likewise, more detailed glomerular or tubular function screening was usually lacking. Zhuang *et al*. retrospectively analyzed renal features in 85 children, and found that 34/85 (40%) had renal involvement to various extents. Nine of them were treated with DPA or zinc, and were excluded from the analysis. Among the remaining 25 patients, 14 had both proteinuria and hematuria, six of them had $\beta$2-microglobulinuria, and four had glycosuria [111]. However, the number of patients with available urinalysis was not clear in the description of the study. Clear phenotyping of the tubular functions is mandatory. For example, subclinical hypercalciuria might occur several years before the diagnosis of WD, and might be responsible for renal stones, nephrocalcinosis, and kidney failure [55, 56]. Hypercalciuria is found in up to 23% (7/31) of patients without treatment, and 37% (3/8) of patients tested after >5 years of therapy [112]. Prevention of urolithiasis relies on dietary evaluation and education, regular ultrasound of CT-scan screening for renal stones, and eventually on urologic surgery and specific therapies such as thiazide diuretics. Calcium, phosphate losses, and poor nutritional state in some WD patients, might lead to osteomalacia and fractures [113]. Renal acidosis is a potent factor that must be looked for to identify patients at risk for bone involvement. In a cross-sectional study conducted at a south Indian care center, the authors recruited 25 consecutive patients with a mean age of 20 (range 12–35), and 50 controls who were age, sex, and BMI-matched, to assess renal tubular acidification and bone mineral density using X-ray absorptiometry [113]. They found that 14/25 (56%) had RTA, 24% of them having distal RTA with metabolic acidosis and incapacity of urine acidification, either spontaneously or after an acid load test (for those without baseline metabolic acidosis). They also had significantly lower bone mineralization (56%) as compared to control participants, especially in patients with RTA. These results are of importance because 21/25 (84%) of these patients were already under DPA or zinc treatment at the time of the study, and, unlike bone demineralization, duration of treatment did not decrease the prevalence of RTA, suggesting that tubular dysfunction might not be as easily reversible as we thought. However, because of the high prevalence of consanguinity in WD (40% of the study population), additional hereditary tubular disorders or rickets cannot be excluded, as it has been previously reported [114].

Finally, renal adverse events under treatment consist mainly in MN after several months of DPA, and are fortunately uncommon under other specific treatments.

Underlying mechanisms of glomerular immune-complex deposition remain to be determined. However, other glomerular manifestations have to be excluded (summarized in Fig. 3). For example, brutal and profound NS suggest similarities to some extent with idiopathic MCD associated with glomerular hyperpermeability, which has also been frequently observed with DPA [95, 101]. Rapid steroid treatment is probably warranted in this subgroup. Otherwise, DPA withdrawal alone and reevaluation should be discussed ahead of moderate proteinuria. Thus, serum albumin, proteinuria, and urinary sediment have to be monitored frequently in WD patients treated with DPA, and nephrology referral, with renal biopsy as a feasibility, is required in case of abnormalities.

## CONCLUSION

The spectrum of kidney involvement in WD is broad and largely understudied. We suggest that all WD patients should undergo regular monitoring of tubular and glomerular functions before treatment and during follow-up. This assessment should annually include screening of serum creatinine, albumin, electrolytes, venous pH, 24-hour urine with electrolytes, glucose, uric acid, amino-acid chromatography, proteins, albumin, fresh urine for urinary density, pH and crystals, and renal ultrasound for kidney morphology and stones. Bone metabolism abnormalities have to be screened with dosage of calcium, phosphorous, vitamin D, calcitriol, PTH, and osteodensitometry preferentially. Prospective studies including extensive and comprehensive nephrological evaluation of WD patients are needed. Interdisciplinary assessment involving nephrologists might optimize their monitoring and provide adequate prevention of further complications.

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## DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

## CONFLICT OF INTEREST STATEMENT

None declared.

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