Type of the Paper (Systematic Review)

Cardiac Involvement in Children with Wilson's Disease

Manal A. ElHawary[1], Doaa B. Abd El Ghafar[1], Sara I. Abo Elnour[1]

[1] Pediatric Department, Faculty of Medicine, Fayoum University, Fayoum, 63514 Egypt.

*Correspondence: Doaa B. Abd El Ghafar, dba11@fayoum.edu.eg, Tel: (002) 01025322608.

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Abstract:

Introduction: Wilson disease (WD) is a rare autosomal recessive disorder caused by mutations in the ATP7B gene, leading to defective copper metabolism. Excess copper accumulation in cardiac tissues can lead to oxidative stress, mitochondrial dysfunction, and direct myocardial toxicity.
Aim of the study: To assess the cardiac involvement in patients suffering from WD.
Subjects and Methods: We searched Cochrane, Web of Science, PubMed, and SCOPUS for relevant articles. We utilized a strategy for our search by combining these keywords: (‘’ Heart’’ OR ‘’ cardiac’’ OR ‘’ cardiovascular’’ OR ‘’ echocardiography’’) AND (‘’ Wilson's disease ‘’). Quality evaluation of the involved studies was assessed regarding to Cochrane’s risk of bias tool.
Results: we found that there was no substantial difference between the control and WD cohorts in terms of left ventricular wall diameters and thicknesses, left ventricular ejection fraction, and left ventricular diastolic function parameters. Regarding left ventricular (LV) ejection fraction, there were no variations between the groups (p = 0.382). There was a notable decrease in tricuspid annular plane systolic excursion, right ventricular (RV) fractional area change, and RV ejection fraction, which measures systolic RV function.
Conclusions: Copper accumulation in cardiac tissues can lead to electrophysiological abnormalities (arrhythmias), cardiomyopathy, autonomic dysfunction, and endothelial damage. These complications, if undiagnosed or untreated, may contribute to an increased risk of cardiovascular morbidity and mortality.

1. Introduction

WD is a rare autosomal recessive disorder characterized by defective hepatic copper metabolism, leading to systemic copper accumulation. While it primarily affects the liver and brain, its impact on the cardiovascular system has gained increasing recognition. Cardiac involvement in Wilson disease is an underappreciated yet significant aspect of the disease, with potential implications for morbidity and mortality [1]. Copper accumulation in cardiac tissues can lead to structural and functional abnormalities, including cardiomyopathy, arrhythmias, and endothelial dysfunction. Dilated cardiomyopathy, although rare, has been

reported in some WD patients, likely due to oxidative stress and direct copper-induced myocardial toxicity. The excessive copper burden can result in mitochondrial dysfunction, apoptosis, and fibrotic remodeling, ultimately impairing cardiac contractility [2].

Arrhythmias are another critical manifestation of cardiac involvement in Wilson's disease. Patients may develop conduction abnormalities such as atrioventricular block, sick sinus syndrome, or ventricular tachyarrhythmias. Copper's toxic effect on the conduction system is thought to be mediated by its influence on ion channels and oxidative stress-related damage to cardiac myocytes. Prolongation of the QT interval has also been noted in some studies, potentially increasing the risk of sudden cardiac death (2). Vascular involvement in WD primarily stems from endothelial dysfunction and altered nitric oxide metabolism. Studies have suggested that increased oxidative stress and lipid peroxidation contribute to endothelial damage, potentially leading to increased arterial stiffness and atherosclerosis. This may predispose WD patients to early-onset cardiovascular disease, although large-scale epidemiological data are limited [3].

While overt heart failure in Wilson disease is rare, subtle cardiac dysfunction can occur. Echocardiographic studies have revealed diastolic dysfunction in some patients, indicating subclinical myocardial impairment. Additionally, left ventricular hypertrophy and systolic dysfunction have been sporadically reported, raising concerns about long-term cardiovascular consequences. The impact of chelation therapy on cardiac manifestations remains an area of interest [4]. Penicillamine and trientine, the mainstays of WD treatment, facilitate copper excretion but may not completely reverse cardiac changes. Zinc therapy, which reduces copper absorption, is often used in maintenance therapy but has not been extensively studied in relation to cardiac involvement. Regular cardiac monitoring, including electrocardiograms and echocardiography, is essential for the early detection of cardiac abnormalities in WD patients [5].

Given the potential for cardiac complications, a multidisciplinary approach is crucial for managing Wilson's disease. Collaboration between hepatologists, neurologists, and cardiologists can ensure comprehensive care and timely intervention. Future research should focus on elucidating the precise mechanisms of copper-induced cardiotoxicity, identifying biomarkers for early detection, and exploring targeted therapeutic strategies to mitigate cardiovascular risks in WD patients [5]. Overall, while hepatic and neurological symptoms dominate the clinical spectrum of Wilson's disease, cardiac involvement should not be overlooked. Early recognition and management of cardiac manifestations can improve patient outcomes and reduce the risk of life-threatening complications. Increased awareness among clinicians and further research into the cardiovascular aspects of WD will be essential for optimizing patient care [6]. Our study aims to assess the cardiac involvement in patients suffering from WD.

2. Subjects and methods

1.1. Information Sources and Search Strategy

We performed this study based on the PRISMA guidelines and recommendations [7]. We utilized a strategy for our search by combining these keywords: (‘’ Heart’’ OR ‘’ cardiac’’ OR ‘’ cardiovascular’’ OR ‘’ echocardiography’’) AND (‘’ Wilson's disease ‘’). Regarding the sources of data, we utilized the Web of Science, Cochrane Library, PubMed, and SCOPUS databases in the search process. We searched these databases till January 2025.

2.2. Study selection

We started by screening the titles and abstracts. We then carried out a full-text screening. Finally, we chose the qualifying articles in accordance with the following eligibility requirements: Case cohort: Individuals suffering from WD, Control cohort: Healthy individuals without WD, Intervention: Assessing the cardiac involvement, and Outcome: heart failure (HF), atrial fibrillation (AF), left ventricular ejection fraction (LVEF), and left ventricular hypertrophy.

2.3. Subjects

Inclusion criteria

We included papers that met our eligibility criteria, which were recent studies above 2010, studies that included both males and females, studies that evaluated the cardiac involvement in individuals with WD, double-arm studies that had case and control cohorts, and articles in English. We chose observational studies and blind or non-blind and non-randomized or randomized controlled clinical trials (RCTs).

Exclusion criteria

We excluded reviews, surveys, and abstracts. Also, we excluded single-arm studies that assessed only one group and studies in languages other than English.

2.4. Quality evaluation

Since we involved five observational studies, we used the Cochrane risk of bias (ROB) assessment that evaluates 14 categories in each clinical study [8]. Each study got a score from 1 to 14, and the overall average score was calculated.

2.5. Data extraction

Two different categories of data were taken from the included papers. The first type includes the demographic information about the patients involved and the data of baseline data for our results. The second type was data on quality assessment. Microsoft Excel was used to carry out the data collection process [9].

3. Results

3.1. Summarization of the involved studies

The results of our search are declared in the PRISMA flow chart **(Figure 1)**. In this systematic review, we involved five studies (10-14) that met the inclusion criteria of our systematic review. Our article involved 254 individuals divided into two cohorts: the case cohort, which involved 127 patients, and the control cohort, which involved 127 healthy individuals. The average age of the included individuals in the case cohort was 10.8 years, while that of the control cohort was 10.2 years. **Table 1** declares the baseline features of the involved individuals and studies.

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Study ID	Country	Study design	Sample size		Age, years (mean)		Male (N)		Female (N)	
			Case	Control	Case	Control	Case	Control	Case	Control
Ertaş 2024	Turkey	A Case-control	20	20	12.8 ± 3.7	11 ± 3.5	10	10	10	10
Karakurt 2016	Turkey	A Case-control	21	20	11.04 ± 3 .58	10.53 ± 2.8	11	9	10	11
Hamdani 2018	Pakistan	A cross-sectional	22	29	11.6±2.23	10.8±2.4	10	18	12	11
Elkiran 2013	Turkey	A Case-control	22	21	11.18 ± 2.83	10.14 ± 2.26	11	10	11	11
Karhan 2019	Turkey	A Case-control	42	37	7.35 ± 3.37		21	18	21	19

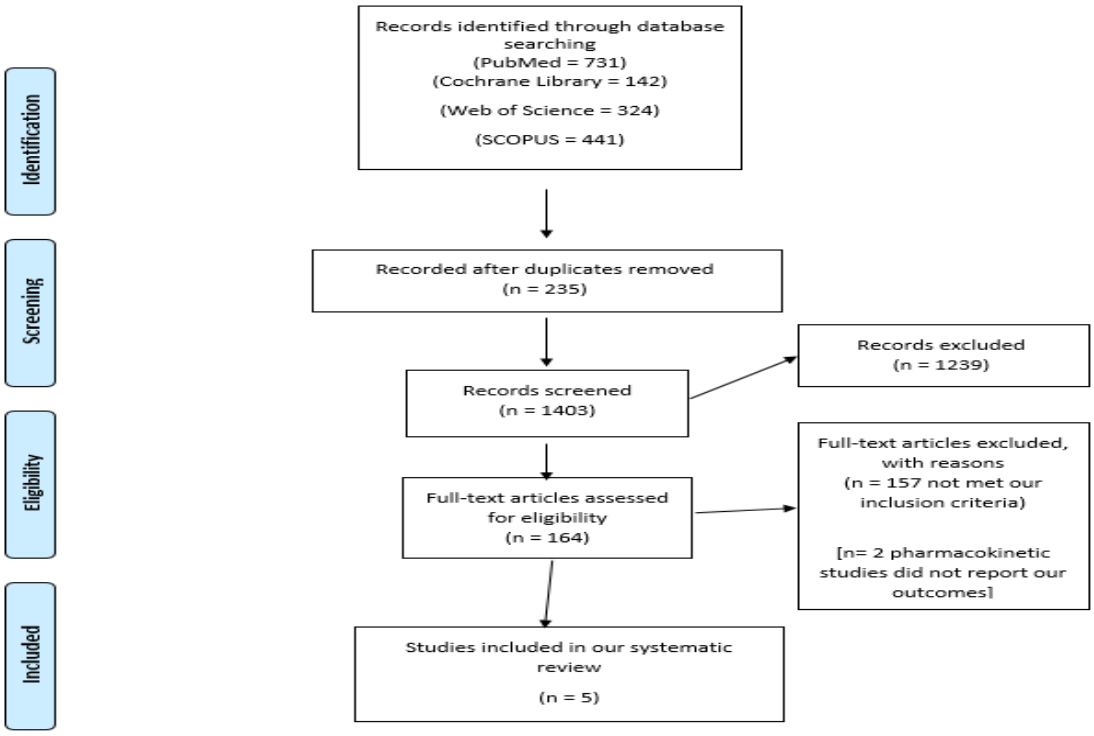

Figure 1: The literature search's PRISMA flow diagram**.**

Results of quality assessment

Since we included five observational studies [10-14], we identified their quality utilizing Cochrane's tool. Cochrane's tool demonstrated that the observational studies' mean score was 10.2 out of 14. The quality explanation of the observational studies is shown in **Table 2.**

Table 2 shows the quality evaluation of the involved studies.

	Ertaş 2024	**Karakurt 2016**	**Hamdani 2018**	**Elkiran 2013**	**Karhan 2019**
1. Was the study's target population clearly identified and defined?	1	1	1	1	1
2. Was the purpose or research question of this work clearly stated?	1	1	1	1	1
3. Did at least half of those who qualified take part?	1	1	1	0	1
5. Were estimates of effect and variance provided, a description of power, or an explanation of sample size?	0	0	0	0	0
4. Were all participants from similar or the same demographics, and did they all take part at the same time?	0	1	1	1	1
7. Was the length such that one could reasonably expect to see it if there was a relationship between exposure and outcome?	1	1	1	1	1
6. Before determining the outcome or outcomes for the study in this paper, were the exposure or exposures intended to be measured?	1	1	1	1	1

9. Were the exposure measurements, or independent variables, applied consistently to every study participant, well-defined, valid, and reliable?	1	1	1	1	1
8. Did the study look at the connection between various exposure levels and results for exposures that can vary in amount or degree (such as exposure categories or exposure evaluated as a continuous variable)?	0	0	1	0	0
11. Were the outcome measurements, or dependent variables, appropriately defined, reliable, valid, and applied uniformly to each research participant?	1	1	1	1	1
10. Were the exposure(s) evaluated more than once over time?	1	1	0	1	1
13. Did the follow-up loss equal the baseline by 20% or less?	1	1	1	1	1
14. Have the effects of significant possible confounding factors on the connection between outcome and exposure been measured?	1	1	0	1	0
12. Were the participants' exposure statuses hidden from those assessing the results?	*	*	*	*	*
Total score (out of 14)	10/14	11/14	10/14	10/14	10/14

*Key: N/A = Not applicable, 1 = Yes, * = Not reported, 0 = No,*

Table 3: The results of the involved studies.

Study ID	Results
Ertaş 2024 [10]	There was no substantial difference between the control and WD cohorts in terms of left ventricular wall diameters and thicknesses, left ventricular ejection fraction, left ventricular diastolic function parameters (deceleration time, A, E, E/A), or tricuspid annular plane systolic excursion. According to tissue Doppler echocardiography, the WD individuals had decreased tricuspid lateral e', mitral septal e', and mitral lateral e' velocities, which were statistically substantially distinct from the controls (p = 0.005, 0.04, and 0.02, respectively). There was no substantial variance in the global longitudinal systolic strain between the WD and control groups. WD patients had a decreased longitudinal early diastolic strain rate, which was statistically significant (p = 0.002).
Karakurt 2016 [11]	Segmental analysis demonstrated significantly lower end-systolic longitudinal displacement in the mid-antero, mid-posterior, and basal posterior-septal segments, as well as reduced end-systolic longitudinal strain in the mid-posterior and posterior segments, and the basal anterior and mid-anterior segments ($p < 0.05$) within the patient group.
Hamdani 2018 [12]	The most common findings were aberrant T waves in 18 individuals (35.2%), followed by sinus bradycardia in 8 patients and sinus tachycardia in 12 individuals. Bifid P waves, two patients' ST segments changing, and one premature ventricular contraction were among the other anomalies. All patients had normal QRS features, including complex, axis, amplitude ratio, and QT interval. During the period of the study, there was no cardiac-related mortality.
Elkiran 2013 [13]	Regarding left ventricular ejection fraction (LVEF), there were no variations between the groups. Out of 61 patients, five had a lower left LVEF than 57%. Although none of the patients displayed symptoms of left ventricular hypertrophy, WD patients had a greater left ventricular (LV) mass than controls. There was a notable decrease in tricuspid annular plane systolic excursion, RV fractional area change, and RVEF, which measures systolic right ventricular (RV) function. Out of 61

	patients, two had lower RVEF.
Karhan 2019 [14]	Both groups underwent equal standard echocardiographic and standard electrocardiographic exams. There was no discernible difference between the two groups' diastolic performance, shortening fraction, or left ventricular ejection fraction. On tissue Doppler echocardiography, the patient group had higher Tei indices for the mitral septal, mitral lateral, tricuspid septal, tricuspid lateral, and interventricular septum; however, these differences did not achieve a statistically significant value. When compared to the control group, the patient group's septal systolic and mitral lateral annular velocity estimates were considerably lower (p = 0.02 and 0.04, respectively). Additionally, the patient group's septal isovolumetric and mitral lateral contraction time values were greater (p = 0.04). While there was no significant difference in the LV values, the patient group's relative wall thickness of LV was greater than the control group's, and 7 (16%) out of 42 patients had concentric remodeling in their left ventricles. The patient group had significantly greater P-wave dispersion values (p = 0.04) and QT interval (p = 0.02) than the control group, which are indicators of arrhythmias.

4. Discussion

Wilson disease (WD) is primarily recognized as a hepatic and neurological disorder caused by defective ATP7B-mediated copper metabolism, leading to systemic copper accumulation. However, growing evidence suggests that WD also affects the cardiovascular system, with potential consequences for morbidity and mortality. This systematic review highlights the various aspects of cardiac involvement in WD, including structural, functional, and electrophysiological abnormalities, as well as the implications for diagnosis and management [15,16].

The myocardial effects of WD primarily result from excessive copper deposition, which induces oxidative stress, mitochondrial dysfunction, and cellular apoptosis. Several studies have reported the presence of dilated cardiomyopathy in WD patients, albeit as a relatively rare complication. The accumulation of copper within myocardial tissues may contribute to myocardial fibrosis, reduced contractility, and left ventricular dysfunction. While overt heart failure is uncommon, subclinical myocardial involvement is more frequently observed [17].

Echocardiographic studies in WD patients have demonstrated subtle alterations in cardiac function, including diastolic dysfunction and changes in left ventricular morphology. Some reports suggest that left ventricular hypertrophy may develop in response to chronic oxidative stress, but there is no clear consensus regarding its prevalence. Additionally, impaired myocardial strain and speckle-tracking

echocardiography findings suggest that WD may induce early myocardial dysfunction before overt clinical symptoms appear [18].

Arrhythmias represent another significant cardiac manifestation in WD. The toxic effects of copper on the cardiac conduction system may lead to various conduction abnormalities, including atrioventricular block, sinus node dysfunction, and prolonged QT intervals. These disturbances may predispose patients to life-threatening arrhythmias, involving sudden cardiac death and ventricular tachycardia [18].

Some studies have reported that QT prolongation is more prevalent in WD patients than in the general population, possibly due to copper's influence on cardiac ion channels and mitochondrial energy metabolism. The impact of copper accumulation on the autonomic nervous system may also contribute to heart rate variability and arrhythmogenesis. However, whether these changes significantly affect long-term cardiovascular outcomes remains uncertain due to limited longitudinal studies [19]. Beyond myocardial and electrophysiological disturbances, WD may also contribute to vascular dysfunction, particularly through its effects on endothelial health. Endothelial cells are highly sensitive to copper-induced oxidative damage, which may impair nitric oxide bioavailability and promote vascular stiffness. Some studies have reported increased arterial stiffness and impaired flow-mediated dilation in WD patients, suggesting a predisposition to early-onset cardiovascular disease [19].

However, it remains unclear whether WD significantly increases the risk of atherosclerosis and ischemic heart disease. While increased oxidative stress is a known contributor to vascular pathology, WD patients often exhibit low cholesterol levels, which may counterbalance the pro-atherogenic effects of endothelial dysfunction. Further research is needed to clarify whether WD patients have an increased long-term risk of cardiovascular events such as myocardial infarction or stroke [20].

Chelation therapy, which is the cornerstone of WD management, plays a critical role in reducing systemic copper burden. However, its impact on cardiac manifestations is not fully understood. Penicillamine and trientine, both copper-chelating agents, are effective in lowering free copper levels but may not fully reverse established myocardial or conduction abnormalities. Some case reports suggest improvement in cardiac function following chelation therapy, while others indicate

persistent cardiac dysfunction despite adequate copper removal [21].

Zinc therapy, which reduces intestinal copper absorption, is often used in maintenance treatment but has not been extensively evaluated for its effects on cardiac involvement. Given that cardiac abnormalities may be subtle and progressive, regular cardiac monitoring with echocardiography and electrocardiograms (ECGs) should be considered in WD patients, particularly those with neurological or systemic manifestations [22].

Despite the growing evidence of cardiac involvement in WD, its clinical implications remain debated. While some patients develop significant cardiac dysfunction requiring intervention, others may have only mild abnormalities that do not progress over time. The variability in cardiac involvement may be related to factors such as disease severity, duration of copper accumulation, and individual genetic differences. Additionally, the impact of chelation therapy on cardiac function is an area of ongoing research. Chelators such as penicillamine and trientine are used to reduce copper burden, and some studies suggest that cardiac abnormalities may improve with effective treatment. However, in patients with long-standing disease or myocardial fibrosis, cardiac dysfunction may persist despite adequate copper chelation [22].

The findings of this systematic review emphasize the need for greater awareness of cardiac involvement in WD among clinicians. Although the primary focus of WD management remains hepatic and neurological complications, cardiovascular assessment should not be overlooked. Regular screening for arrhythmias, subclinical myocardial dysfunction, and vascular abnormalities can help identify at-risk patients and guide early intervention [22]. Future studies should aim to clarify the exact mechanisms of copper-induced cardiotoxicity, identify potential biomarkers for early detection, and explore targeted therapies to mitigate cardiovascular complications. Additionally, large-scale longitudinal studies are needed to determine the long-term cardiovascular prognosis of WD patients and assess whether chelation therapy significantly alters cardiac outcomes.

5. Conclusion

Copper accumulation in cardiac tissues can lead to electrophysiological abnormalities (arrhythmias), cardiomyopathy, autonomic dysfunction,

and endothelial damage. These complications, if undiagnosed or untreated, may contribute to an elevated risk of cardiovascular mortality and morbidity. While cardiac involvement in WD is less commonly recognized than hepatic and neurological manifestations, it is a clinically significant aspect of the disease with potential implications for morbidity and mortality. A multidisciplinary approach involving hepatologists, neurologists, and cardiologists is essential to ensure comprehensive care for WD patients and improve long-term outcomes.

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