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WILSON'S DISEASE: A MULTISYSTEMIC CONDITION CAUSED BY ABERRANT COPPER ACCUMULATION, INCLUDING ITS PATHOGENESIS, EPIDEMIOLOGY, PRESENT STATE, AND EFFECTIVE TREATMENT APPROACHES

Yash Srivastav[1*], Jyotsana Shrivastava[2], Madhaw Kumar[3], Nutan Shrivastava[4], Nikita Sharma[5], Anubha Dhuriya[6], Mohammad Aqil Siddiqui[7]

[1]Assistant Professor, Shri Venkateshwara University, Gajraula, Uttar Pradesh, India.
[2]Dr. Rammanohar Lohia Avadh University, Uttar Pradesh, India.
[3]Goel Institute of Pharmacy & Sciences, Lucknow, Uttar Pradesh, India.
[4]City Women's College, Jankipuram, Lucknow, Uttar Pradesh, India.
[5]Signa College of Pharmacy, Kanpur, Uttar Pradesh, India.
[6]Aryakul College of Pharmacy and Research, Lucknow, Uttar Pradesh, India.
[7]Lucknow College of Pharmacy, Lucknow, Uttar Pradesh, India.

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***Corresponding Author: Yash Srivastav**
Assistant Professor, Shri Venkateshwara University, Gajraula, Uttar Pradesh, India.
ORCID Id: https://orcid.org/0009-0008-5017-6529 **DOI:** https://doi.org/10.5281/zenodo.17484950

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ABSTRACT

Wilson's disease (WD) is an uncommon autosomal recessive copper metabolism disorder brought on by ATP7B gene mutations. This gene produces the ATP7B protein, a crucial transmembrane copper-dependent ATPase that is mostly expressed in hepatocytes. ATP7B is necessary for the liver's two primary vital copper metabolism routes, which are (1) copper incorporation into ceruloplasmin (Cp) and (2) hepatocyte biliary excretion of excess copper. Copper will gradually and pathologically build up, mostly in the liver but also in other tissues, including the cornea and central nervous system, whenever ATP7B is lost or its function is diminished in hepatocytes. Wilson's disease affects roughly one in 30,000 individuals. Typically, symptoms start to appear between the ages of five and thirty-five. It bears the name of British neurologist Samuel Wilson and was initially reported by German pathologist Friedrich Theodor von Frerichs in 1854. According to the World Health Organisation, between 10 and 30 million people worldwide suffer from Wilson disease, with an incidence of 1 in 10,000 to 30,000 persons. 2–5 Orphanet estimates that the prevalence varies by geographic location, ranging from 1 to 9 per 100,000 people worldwide. According to the World Health Organisation (WHO), between 30 and 100 cases of WD occur worldwide. In a study of hepatobiliary spectrum illnesses in North India, WD impacted 7.6% of cases. Despite the absence of epidemiological data on neurological WD in India, a South Indian WD clinic reported 15–20 new cases of WD annually. Wilson's disease is characterised by a wide range of clinical signs and symptoms, from acute liver failure and severe neurological symptoms to asymptomatic liver involvement. The recommendations provide customised diagnostic methods for particular presentations, such as severe failure of the liver. Wilson disease patients require treatment for the rest of their lives. Acute liver failure may result after stopping treatment. Blood and urine tests are routinely performed by doctors to assess the effectiveness of treatment. Wilson disease is treated with two chelating agents: trientine (Syprine) and penicillamine (Cupramine, Depen). Copper is eliminated from the body by these medications. Management of Wilson Disease: The American Association for the Study of Liver Diseases' 2022 Practice Guidance on Wilson Disease offers a modern method for WD diagnosis and treatment. It takes the place of earlier AASLD guidelines on the same subject that were released in 2008. Being listed in an NLM database does not mean that NLM or the National Institutes of Health agree with or approve the information. A mutation in the ATP7B gene causes Wilson's disease (WD), an autosomal recessive condition that mostly affects the liver and brain and results in impaired copper metabolism. Wilson's disease (WD) pathophysiology, aetiology, diagnosis, treatment, and consequences are all covered.

KEYWORDS: Wilson's disease (WD), Epidemiology, Aetiology, Treatments, Pathophysiology.

INTRODUCTION

One hundred years after being first described by Kennear Wilson in 1912, our understanding of Wilson's disease diagnosis and treatment reflects its prevalence as a rare disease, primarily based on expert opinions and the use of pharmaceutical agents without the rigorous randomised clinical trials that are the cornerstone. Early detection and intervention are critical and can save lives. The clinical consequences of Wilson's disease (WD), which is caused by a defective ATP7B protein product, range from asymptomatic to fulminant hepatic failure, chronic liver disease with or without cirrhosis, and neurological and psychiatric manifestations. WD is characterised by impaired copper metabolism. It is necessary to have a high level of suspicion to detect WD, particularly in less florid instances with limited neuropsychiatric involvement or only a slight rise in transaminases. Hepatolenticular degeneration, also known as Wilson disease, is a rare autosomal recessive condition caused by gene mutations that lead to excessive copper accumulation in the liver, brain, cornea, and other organs.[1] Hepatic and neuropsychiatric symptoms, such as jaundice, liver failure, tremors, mood swings, and movement problems, are the main manifestations of Wilson's disease. Mutations in the ATP7B gene cause Wilson disease, sometimes called hepatolenticular degeneration, a rare autosomal recessive condition that results in aberrant copper accumulation in the liver, brain, cornea, and other organs. This disorder mostly affects the liver, brain, cornea, and lens, but it can also affect other organ systems, such as the kidneys (producing proximal renal tubular dysfunction), the bones (causing arthritis), and the heart (causing nonischemic cardiomyopathy). The neurological and hepatic systems are the main sources of overt symptoms. Jaundice, pruritus, nonspecific nausea, vomiting, and oedema in the lower extremities are all signs of liver disease. The main cause of jaundice is concomitant haemolytic anaemia. Neuropsychiatric symptoms such as tremors, hypophonia, dysarthria, anxiety, mood or personality disorders, and visual or auditory hallucinations are examples of extrapyramidal symptoms. The majority of Wilson disease patients exhibit neuropsychiatric symptoms in their third or fourth decade of life, followed by liver-related symptoms in their first decade. Wilson's illness is uncommon but can be lethal if left undiagnosed or untreated. Usually, eye exams, liver biopsies, and serologic and urine testing are used to diagnose the illness. Wilson's disease can be lethal if left untreated, especially if acute liver failure occurs. In order to decrease copper absorption, treatment entails zinc supplementation and copper chelation therapy with substances like D-penicillamine and trientine. Liver transplantation may be required in extreme circumstances. Novel chelators and gene therapy techniques are examples of emerging therapeutics that are being researched.[2,3] Improving patient outcomes requires early discovery and ongoing care. New developments in diagnostic methods present encouraging ways to get over these restrictions. Relative exchangeable copper (REC) and ATP7B protein measurement in dried blood spots are two novel biomarkers that have shown increased accuracy in differentiating WD from other diseases. Non-invasive techniques for identifying early disease-related alterations are offered by advanced imaging modalities as copper-64 positron emission tomography (PET) imaging, anterior segment optical coherence tomography (AS-OCT), and quantitative susceptibility mapping (QSM). Additionally, next-generation sequencing (NGS) improves family screening and genetic screening, enabling earlier diagnosis. Improving early detection and patient outcomes requires a thorough strategy that integrates traditional and cutting-edge diagnostic techniques. Enhancing diagnostic precision, cutting down on delays, and improving treatment plans for WD can be achieved through increased understanding of the limitations of conventional testing and the integration of innovative biomarkers and imaging methods into clinical practice. In WD, Kayser-Fleischer rings KF rings have a special role in WD diagnosis. Their limitations necessitate a sophisticated understanding, even though their presence can be a useful hint. KF ring detection in WD is essential for prompt diagnosis and therapy start. 3. KF rings are seen in 20–30% of patients with pre-symptomatic WD, 40–50% of

individuals with hepatic WD, and almost 90% of patients with neurological WD. Dark rings that seem to encircle the eye's cornea are known as Kayser-Fleischer rings. These are caused by specific liver illnesses that result in copper buildup in the Descemet's membrane. They bear the names of the German ophthalmologists Bruno Fleischer and Bernhard Kayser, who originally characterised them in 1902 and 1903.[4]

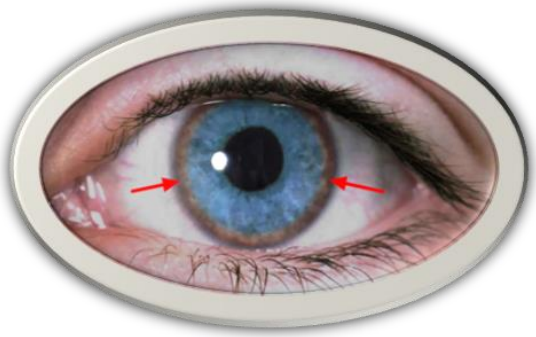

Fig. 1: Kayser–Fleischer Ring.

(A shadowy circle that seems to surround the eye's iris)

Mutations in ATP7B cause Wilson's disease, an autosomal recessive illness of copper metabolism that manifests in neurological, psychiatric, ophthalmological, and hepatic symptoms. Neurological results are still inconsistent despite the use of decoppering treatments to stop the progression of the disease and lessen its symptoms. With an emphasis on recent developments, we examine the pathophysiology, biomarkers, and therapies for Wilson's disease from a neurological standpoint in this article. Although the genetic and molecular pathways behind ATP7B failure have been thoroughly described, it is still unknown why only a small percentage of patients experience neurological or psychiatric symptoms, even after much work has been done to find genotype–phenotype connections. Hepatic, neurological, psychiatric, ophthalmological, haematological, renal, and rheumatological symptoms can all be found in Wilson's disease, an autosomal recessive illness of copper metabolism. Given that no single test can confirm or rule out the condition and since diagnostic delays are frequent, making a diagnosis can be difficult. Adverse effects, such as unexpected neurological deterioration, might happen, and treatment regimens differ. Innovative Treatments and Prospects: Trials are being conducted on trientine tetrachloride, a more recent version of trientine with better pharmacological and pharmacokinetic characteristics. In a phase 1 single-dose research, this treatment showed higher absorption rates than conventional trientine, which led to higher systemic bioavailability. In a phase 3 randomised clinical trial, the CHELATE trial showed that trientine tetrachloride was not inferior to D-penicillamine in preserving stable nonceruloplasmin-bound copper throughout a 24-week follow-up. Trientine tetrachloride was authorised by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for use in Wilson disease patients. A once-daily version of trientine tetrachloride is currently undergoing trials to assess its safety and effectiveness, since it may be a useful tactic to lower the need for repeated doses and improve patient adherence. Wilson's disease has a genetic origin; thus, gene-correction therapies are still an option. utilizing gene-corrected patient-specific induced pluripotent stem cell (iPSC)-derived hepatocytes (iHeps) and CRISPR/Cas9, this has been successfully investigated to restore ATP7B function in vitro and in vivo in a mouse model utilising hepatocytes obtained from a patient with Wilson disease. The adeno-associated serotype 8 vector (AAV8) has been used to restore copper metabolism in mouse models through a different route; however, the gene size was too large, which limited the vector's ability to spread. We offer a useful manual for Wilson's illness in this review.[5-7]

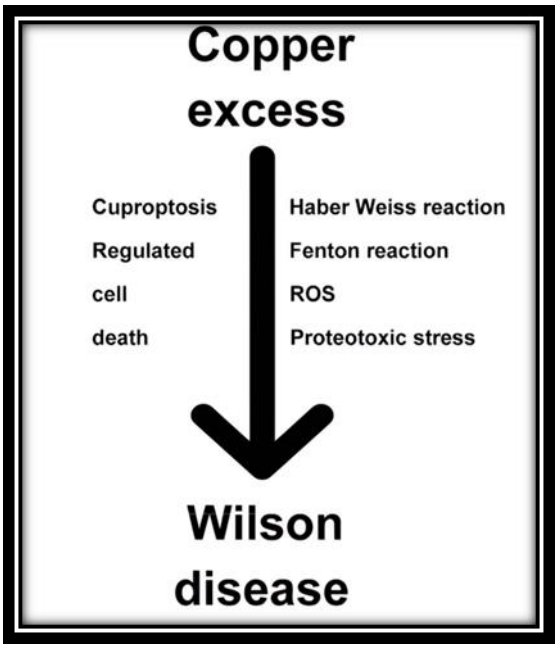

Fig. 2: Wilson's disease (WD).

HISTOPATHOLOGY

When a patient has a liver biopsy after initial serologic and urine testing are equivocal, conventional light microscopy may show a variety of pathologic abnormalities that are typical of other hepatic disorders. In metabolic dysfunction-associated steatotic liver disease (MASLD), fatty infiltration with Mallory Hyaline bodies and steatohepatitis may be observed in liver biopsies (see Image Wilson disease). Interface hepatitis, which is commonly observed in autoimmune hepatitis, may also be detected by biopsy. Copper deposits are identified using the rhodanine stain. If the hepatic copper concentration is more than 250 µg/g dry weight (about 4 µmol/g dry weight), Wilson's disease is diagnosed. A normal hepatic copper concentration usually falls between 15 and 55 µg/g dry weight.[8,9]

EPIDEMIOLOGY

The disease has a carrier frequency of 1 in 90 people and affects 1 in 30,000 people. Patients with Wilson's disease exhibit an equal preference for males and females. Although it often manifests during the first and fourth decades of life, it has been found in individuals as old as 70 and toddlers as young as 3. With a gene frequency of 0.56% and a carrier frequency of 1 in 90, the prevalence of WD, a rare disease, is comparable in most parts of the world, amounting to roughly 0.5 instances per 100,000 people, or the most common figure of 30 cases per million. However, in some regions or nations, the disease is considerably less common, and certain mutations are reported to occur more commonly in particular populations. Since there are fewer clinically evident cases compared to the frequency of allele carriers in the community, the more than 500 mutations that have been discovered thus far most likely represent the decreased penetrance of mutations. The most prevalent mutations are Met645Arg in Spain, Arg778Leu in South Korea, Japan, and China, 2007del7 in Iceland, and His1069Glu (H1069Q) throughout Europe and North America. The countries with the highest rates of the disease include Austria (3.0/100000), Japan (3.3/100000), and Germany (2.5/100000). However, Costa Rica has the highest incidence in the world (4.9/100000 inhabitants; see the section below on perspectives from high-incidence countries). This could be because of a higher degree of consanguinity and a potential founder effect; the most common mutant is Asn 1270 Ser, which was previously only identified in Sicilian, Lebanese, and Turkish populations. A well-known founder mutation (-441/-427del) is extremely common (67%) in

Sardinia, the other region of the globe with a very high incidence (estimated 1/10000-1/7000), while all other mutations are present with a relative frequency below 10%. With 1.311 billion people, India is expected to have a sizable population that is afflicted by even a rare hereditary condition like Wilson disease (WD). WD is the most common cause of chronic liver disease in older children, with reports coming from all over India. However, if the disease is detected early on, treatment intervention can effectively control this potentially fatal condition, which shares symptoms with various neurological and hepatic disorders.[10] As this chapter explains, the opportunity is provided by the identification of mutations in the disease-causing gene in various regions of India. The clinical variability of WD makes it difficult to rigorously correlate genetics to phenotype, as this Indian study also shows. A mutation in the ATP7B gene causes Wilson's disease (WD), an autosomal recessive condition that mostly affects the liver and brain and results in impaired copper metabolism. Early identification and appropriate management of WD can lead to a nearly full recovery because it is a curable illness. Over the past 50 years, it has drawn a lot of attention, with notable Indian contributions. Many case series from India raise the possibility that WD is more common than previously believed. In India, the ATP7B mutation p.C271X is frequently found. Later studies were characterised by neuropsychiatric and hepatic signs, although the earliest Indian collection indicated a considerable osseomuscular appearance. In the Indian series, there is a noticeable masculine predominance. Compared to neurological or osseomuscular WD, pure hepatic presentation begins earlier. Nearly 50% of Indian WD patients with a high percentage of consanguinity may have a good family history. With an average diagnostic delay of up to two years, up to two-thirds of cases in India may be misdiagnosed at first. More than four out of five instances have been found to have abnormal 24-hour urine copper and serum ceruloplasmin levels. In almost all cases of neurological WD, the brain MRI is abnormal. The most used chelator in India is D-penicillamine, and copper chelation is still the cornerstone of treatment. The Global Assessment Scale for WD is a thorough clinical monitoring instrument. Up to 90% of neurological WD cases in India return to their pre-morbid functionality with appropriate treatment, whereas hepatic presentations have a five-fold higher death risk.[11-14]

ETIOLOGY

A mutated gene inherited from each parent is the cause of Wilson's illness. You will be a carrier but not afflicted with the disease if you inherit only one faulty gene. This implies that your offspring may inherit the impacted gene. One of numerous mutations in the ATP7B gene, which codes for the ATP7B protein transporter on the long arm of chromosome 13 (13q), which is in charge of excreting excess copper into bile and out of the body, causes Wilson disease, an autosomal recessive disorder. Hepatocytes' trans-Golgi network contains this protein transporter. The majority of patients are compound heterozygotes, which means they have two distinct mutations, one on each chromosome, out of the more than 300 mutations that have been identified. The liver is the main organ via which copper is eliminated. Before being transferred to other organ systems, the extra copper first builds up in the liver and then in the blood. Additionally, too much copper causes free radicals to be produced, which oxidise essential proteins and lipids. Usually, early cellular alterations take place in the peroxisomes, nucleus, and mitochondria. Wilson's illness is inherited, but symptoms don't show up until the liver, brain, eyes, or another organ accumulates copper. The parts of your body that the sickness affects determine the symptoms. If your parents or siblings have Wilson's disease, you may be more susceptible to the illness yourself. To determine if you have Wilson's disease, ask your doctor if genetic testing is necessary. The likelihood of a successful course of treatment is significantly increased by making the diagnosis as soon as possible. Wilson's disease can occasionally result in death if left untreated.[15] Serious issues consist of: Cirrhosis is another name for liver scarring. Scar tissue develops in the liver when liver cells attempt to repair damage brought on by elevated copper levels. The liver has a tougher time functioning as a result liver failure. This can happen

all at once and is referred to as decompensated Wilson's disease or abrupt liver failure. It may also develop gradually over several years. One possible course of treatment is a liver transplant persistent problems with the neurological system. When Wilson's illness is treated, symptoms like tremors, involuntary muscle movements, awkward walking, and difficulty speaking normally get better. However, even after treatment, some people continue to have issues with their nervous systems kidney issues. Kidney damage from Wilson's disease can result in problems, including kidney stones and an abnormally high amount of amino acids eliminated from the urine mental health conditions. These could include psychosis, bipolar illness, irritability, depression, or personality changes issues with the blood. One of them could be hemolysis, or the breakdown of red blood cells. Jaundice and anaemia result from this.[16-18]

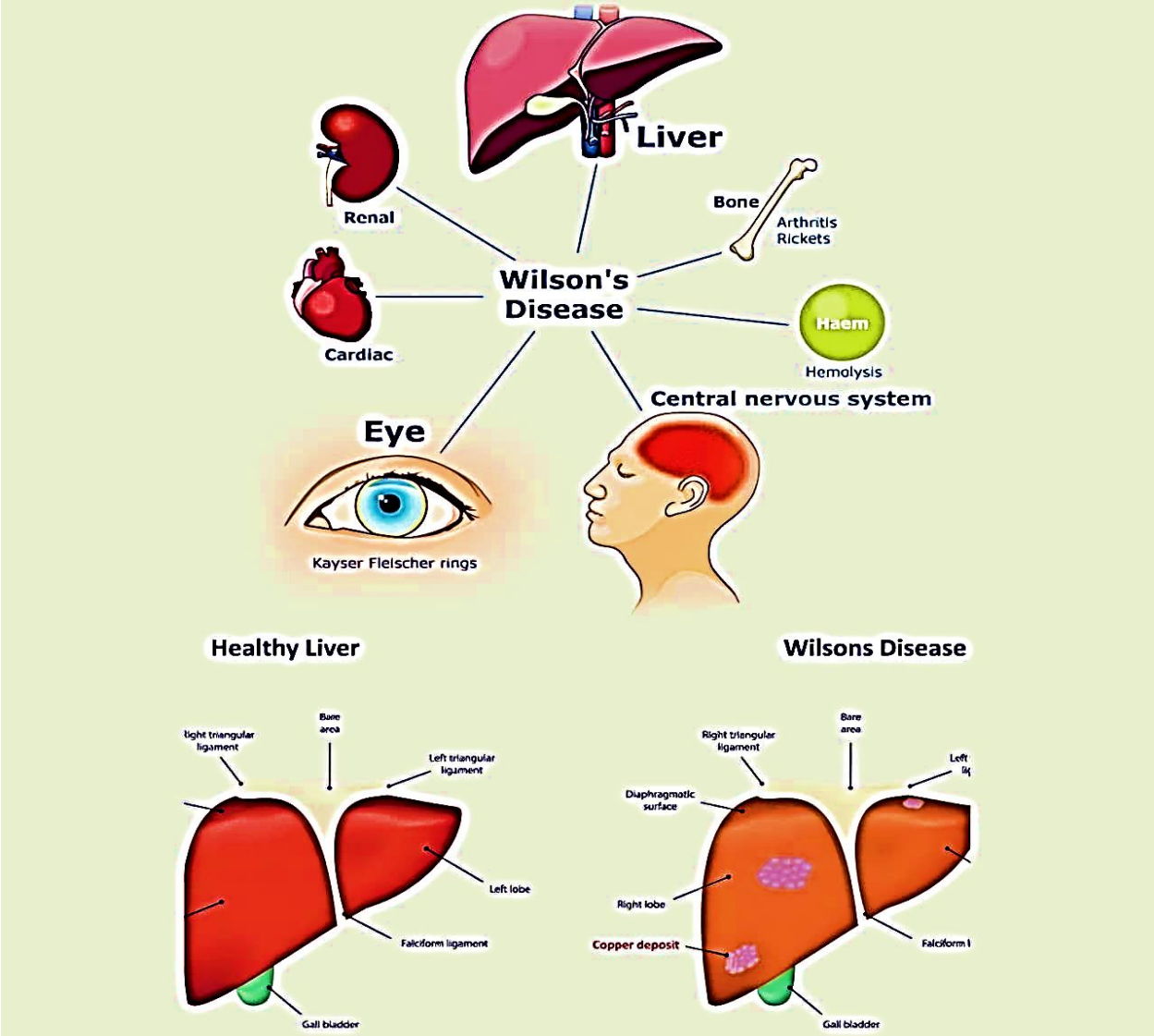

Fig. 3: The effects of Wilson's disease (WD) on the major organs.

PATHOPHYSIOLOGY

Excess copper builds up in the liver and leaks into the bloodstream due to malfunctioning copper excretory systems, where it accumulates in many organs and tissues, especially the kidneys, eyes, and brain. Excess copper then causes a toxic hydroxyl group to form, which increases oxidative stress in the cells and damages tissue. This can lead to clinical symptoms such as movement disorders, liver failure, neuropsychiatric symptoms, and corneal Kayser-Fleischer (KF)

rings, as well as organ dysfunction. A necessary mineral, copper is mostly used as a cofactor for enzymes such as tyrosinase, ceruloplasmin, cytochrome c oxidase, dopamine beta-hydroxylase, and superoxide dismutase. Through the small intestine's transporter proteins, particularly copper transporter 1 (CTR1; SLC31A1), copper enters the body through the digestive tract. This transporter makes it easier for copper to enter cells, where it is attached to metallothionein (19,20). An antioxidant copper chaperone (ATOX1) transports a portion to the trans-Golgi network. ATP7B releases copper into the portal vein, which travels to the liver, in reaction to increasing intracellular copper levels. The metalloenzymes are carried by hepatocytes, where ATOX1 binds within the cell. The excess copper is then eliminated by secreting it into bile after ATP7B binds the copper to ceruloplasmin and releases it into the bloodstream. Copper builds up in the liver as a result of ATP7B malfunction in Wilson disease, and ceruloplasmin is released in a copper-deficient form that is quickly broken down in the circulation. Oxidative damage results from the formation of reactive oxygen species when the liver's copper content surpasses that of naturally bound proteins. Serum transaminases, particularly aspartate transaminase (AST) and alanine transaminase (ALT), are elevated as a result of this damage, which also causes active hepatitis and fibrosis. Despite hepatic inflammation, the alkaline phosphatase (ALP) is often low or normal. Several theories have been put out, although this is still not entirely understood. Zinc is a required cofactor for the metalloenzyme ALP. According to studies, copper may cause a conformational shift in the metalloenzyme, which lowers serum levels, and it may also displace zinc, which reduces ALP function. As will be covered below, the increase in serum bilirubin is frequently indirect and linked to hemolysis. A low serum ALP and a high total bilirubin (TB) level are two of the presentation's main serologic characteristics. As a result, the ALP: TB ratio is less than 4, and the sensitivity and specificity are 94% and 96%, respectively. Ceruloplasmin-free copper is released into the bloodstream by the liver. The brain, kidneys, and eyes are among the organs where this free copper is stored. Copper deposits in the brain's putamen, globus pallidus, and basal ganglia are implicated in neurocognitive functions like mood control and movement coordination. KF rings are caused by the buildup of free copper in the cornea, while sunflower cataracts are caused by the buildup of free copper in the lens. The condition's prominent indirect hyperbilirubinemia and overt jaundice are brought on by intravascular hemolysis, which is caused by oxidative damage to erythrocytes brought on by the buildup of free copper in the blood.[21-24]

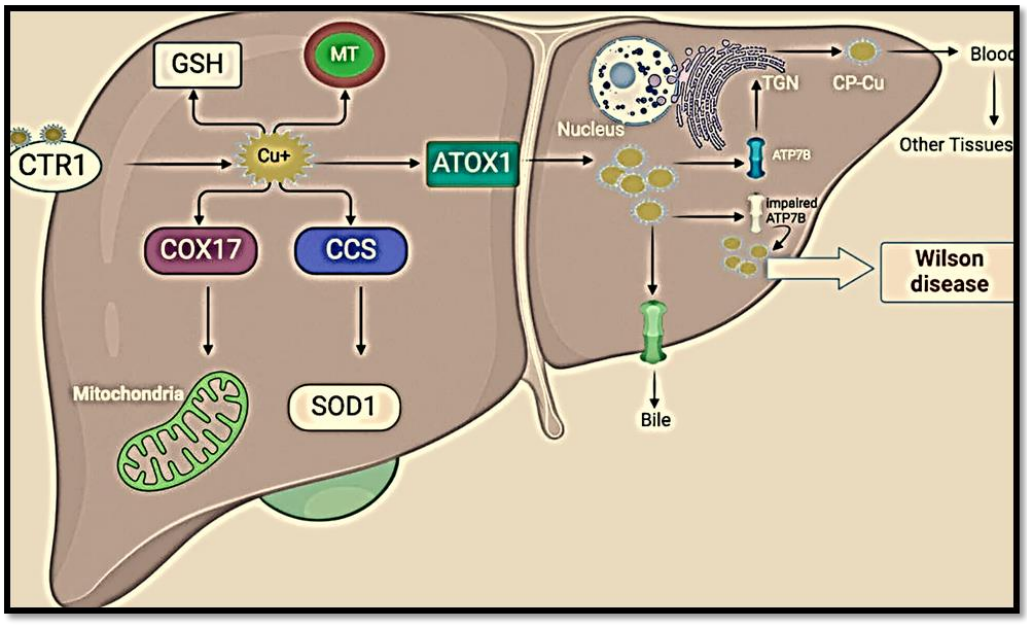

Fig 4: The physiopathology of Wilson's disease (WD)

DIAGNOSIS OF WILSON'S DISEASE

Laboratory Studies: Wilson's disease usually manifests before the age of fifty and is a rare cause of liver disease. People with chronic liver disease are frequently examined for this illness, which is especially crucial for those who develop liver disease earlier in life. However, if the patient has a history of neuropsychiatric symptoms or an ALP: TB ratio of less than 4, Wilson's disease should also be strongly suspected. Wilson's disease can be diagnosed using several different methods. An ocular examination, urine tests, and serologic testing are usually included in the diagnostic methodology. Serum ceruloplasmin is the first serologic test that is advised; an abnormality is indicated by a level of less than 20 mg/dL. Ceruloplasmin testing alone has a low negative predictive value (between 35 and 50 per cent) and a low positive predictive value (between 0.6 and 8 per cent). Serum ceruloplasmin levels may be low in other types of chronic liver disease. A 24-hour urine copper evaluation should be performed on the patient if the ceruloplasmin level is less than 20 mg/dL. An anomaly is indicated by a level greater than 40 µg, usually greater than 100 µg.[25] A ceruloplasmin level below 5 mg/dL indicates aceruloplasminemia, a condition where the ceruloplasmin gene is mutated, leading to cerebral iron accumulation and ceruloplasmin absence. Hepatic copper quantification, urinary copper excretion (in the absence of acute hepatitis), mutation analysis, and the presence of typical clinical signs and symptoms, such as KF rings, neurologic symptoms, serum ceruloplasmin, and Coombs-negative hemolytic anaemia, are all part of the Leipzig scoring system, which was previously proposed. The diagnosis is established with a composite score of 4 or greater. Additional Diagnostic Procedures: To check for KF rings and sunflower cataracts, patients should additionally have a slit-lamp examination performed by an ophthalmologist. Wilson's disease is diagnosed by abnormal KF rings, 24-hour urine copper levels, and ceruloplasmin levels. The patient should get a liver biopsy with copper quantification if they have two of the three serologic abnormalities or if another diagnosis is suspected. Wilson's disease is diagnosed if there is more than 250 µg/g dry weight of copper. If the patient's hepatic copper level is between 50 and 250 µg/g dry weight, molecular tests should be performed. When neurologic symptoms are present, people should be evaluated using brain magnetic resonance imaging (MRI) to check for cerebral involvement. On the T2 sequence, this usually shows hyperintensities in the putamen, globus pallidus, and basal ganglia, which are indicative of heavy metal deposition. Right ventricular hypertrophy and nonspecific alterations to T-waves and ST segments may be seen on an ECG. Because of the possibility of compound heterozygosity, molecular testing is generally not advised as a first-line assessment of Wilson disease. Molecular testing should be used to screen for Wilson's disease in first and second-degree relatives of patients who have been diagnosed.[26-28]

WILSON'S DISEASE: MANAGEMENT AND TREATMENT

Physical and occupational therapy: These treatments are helpful for the disease's neurological component. It could take several months for the neurologic recovery and improvement to show after the copper-chelating treatment. In addition to preventing contractures that may arise from chronic dystonia, these treatments can help with ataxia, dystonia, and tremors. Alternative Medicines, Limitation of copper exposure: It's critical to stop any further copper intake, whether deliberate or inadvertent. For information on foods high in copper, such as organ meats, mushrooms, and chocolate, people should be referred to a nutritionist. It is recommended that patients refrain from using cookware and equipment coated in copper. Check the copper concentration of the water you drink from a well. It is advised to flush copper plumbing and pipes in a person's home by running water through them before using them.[29-30] For Wilson's disease, dietary copper restriction alone is usually insufficient. Pharmacologic Therapies; Chelation: Copper chelation is the cornerstone treatment for nonfulminant Wilson disease and ought to be used for patients with any level of organ involvement. Those who receive a screening-based diagnosis might think about nonchelation treatments. There are

numerous chelators available, such as trientine and D-penicillamine. During the first three weeks of treatment, neurologic symptoms may get worse with any chelating agent; stopping treatment is not advised. Given the decreased intestinal bioavailability when given with food, both should be given either one hour before or two hours after meals. Iron and zinc may also be chelated by chelation therapy, which is not limited to copper. Patients who are pregnant or having surgery should have their dosages reduced because of the possibility of poor wound healing. Titrating oral copper chelation dosage is necessary to reach 24-hour urine copper levels greater than 100 μg. The cost of the medication, the patient's comorbidities, clinical experience, the agent's safety profile, and availability should all be taken into consideration when selecting a copper chelation agent. It is deemed safe to use any copper chelator when pregnant or nursing. Trientine promotes the excretion of copper in the urine while blocking its absorption in the intestines.[31-33] It is recommended to separate trientine and iron by at least two hours since they can generate a hazardous compound when taken together. Aplastic anaemia and gastritis are two of the negative consequences of trientine. Dosing for the first course of treatment starts at 15–20 mg/kg/day (maximum 1500 mg/day) in two or three separate doses, and is then increased over two to three weeks to a maximum of 2000 mg/day. The target dose for maintenance is lowered: 10 to 15 mg/kg/day in divided doses for adults and 20 mg/kg/day (rounded to the nearest 250 mg) in divided doses for children. Adverse effects were more likely to occur at doses greater than 20 mg/kg/day. Copper excretion in the urine is increased by D-penicillamine. If any negative early sensitivity reactions, such as fever, rash, or proteinuria, are observed, D-penicillamine should be stopped right away. Aplastic anemia, thrombocytopenia, and elastosis perforans serpingosa are other side effects. Trientine therapy should be considered for patients with severe thrombocytopenia and chronic kidney disease (CKD), as they are more susceptible to toxicity. Because D-penicillamine is linked to pyridoxine (vitamin B6) inactivation, doctors advise taking 25–50 mg of it daily as a supplement. To reach 1000 to 1500 mg/day (maximum 2000 mg/day) in two to four divided doses, the initial therapy should begin at 250 to 500 mg/kg/day and be raised by 250 mg increments every four to seven days. Adult maintenance therapy is lowered to two divided doses of 750–1000 mg per day. For children, split dosages of 20 mg/kg/day are advised. Evaluating Response to Therapy: It is advised to routinely monitor 24-hour urine copper excretion, liver biochemistries, INR/PT, complete blood count, routine urinalysis, serum copper levels, and ceruloplasmin during chelation therapy. Maintenance therapy should show a 24-hour urine copper of 150 to 500 μg (2.4-8 μmol), while the initial response to copper chelation with either trientine or D-penicillamine should show a 24-hour urine copper of 1000 to 2000 μg (16-32 μmol). A slight 24-hour urine copper excretion, if any, may be observed with zinc monotherapy. Nonchelation: Copper stool excretion rises as a result of oral zinc interfering with enteric copper absorption. Zinc is not usually administered as a monotherapy, but rather as a mainstay therapy after treatment with various copper chelators. Serum lipase and amylase levels may temporarily rise as a result of zinc supplementation without any radiographic or clinical signs of pancreatitis. Adults and children over 50 kg should take 150 mg daily in divided doses as part of their initial treatment. Children under 50 kg and older than 5 years should get divided doses of 75 mg every day. A daily dosage of 50 mg in divided doses should be given to children under 50 kg and under 5 years old. Liver transplantation: Patients who exhibit ALF as a symptom of acute Wilsonian hepatitis should be assessed immediately at a liver transplant facility. It is curative to have a liver transplant.[34-38]

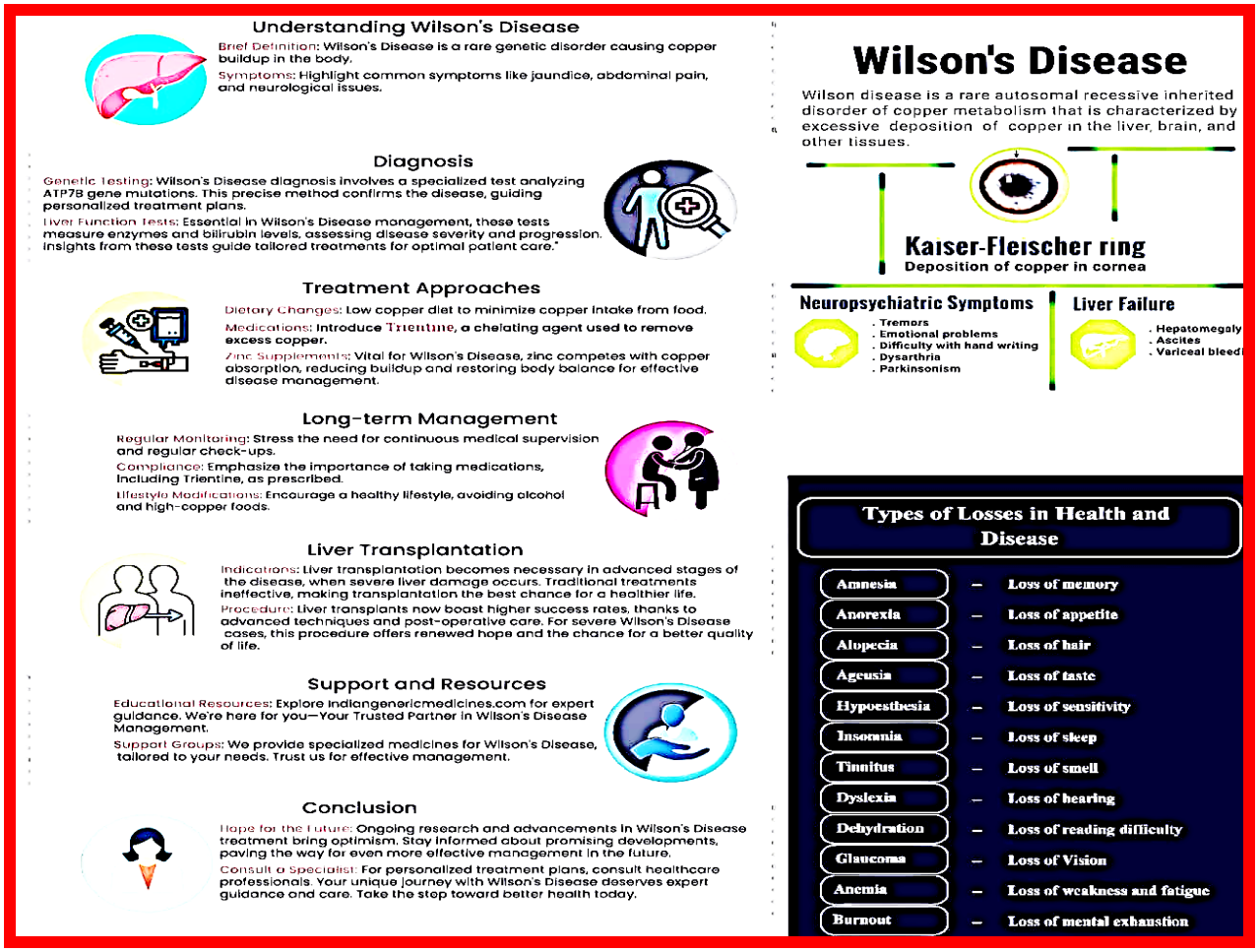

Fig. 5: Wilson's disease (WD) management, identification, and treatment procedure.

DISCUSSION AND CONCLUSION

Our review papers address the pathophysiology, epidemiology, diagnostics, alternative therapeutics, and other causes of Wilson's disease in addition to providing a broad summary of the condition. Our findings suggest that additional clinical research is necessary because of the intricacy of Wilson's disease, which is the most rare and severe disease in the world, even though it can be treated with targeted medications and other therapies. More randomised controlled studies are required to treat Wilson's disease. In the future, we hope to offer an initial evaluation of Wilson's disease. With the assistance of our colleagues, future counselling-based research in our state or country will assess patients' mental and physical health to deliver more precise information regarding Wilson disease and their treatment.

ETHICAL STATEMENT

A pharmacist must behave honorably and truthfully. A pharmacist abstains from behaviors that compromise their commitment to acting in the best interests of their patients, such as unlawful behavior, discriminatory acts, and unfavorable working conditions that impair judgment. A pharmacist maintains their level of proficiency.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors attest that they are free of any known financial or personal conflicts of interest that would taint the findings of this study.

INFORMED CONSENT

Using websites, review articles, and other sources to produce research content.

REFERENCES

1. Schilsky ML, Roberts EA, Bronstein JM, et al. A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases. Hepatology 2022; (online ahead of print). Doi: 10.1002/hep.32801.
2. Roberts EA, Schilsky ML. Current and emerging issues in Wilson's disease. N Engl J Med, 2023; 389(10): 922–938.
3. Zimbrean PC, Schilsky ML. Psychiatric aspects of Wilson disease: a review. Gen Hosp Psychiatry, 2014; 36(01): 53–62.
4. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. Liver Int, 2003; 23(03): 139–142.
5. European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol, 2012; 56(03): 671–685.
6. Socha P, Janczyk W, Dhawan A, et al. Wilson's disease in children: a position paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr, 2018; 66(02): 334–344.
7. El Balkhi S, Poupon J, Trocello JM, et al. Determination of ultrafiltrable and exchangeable copper in plasma: stability and reference values in healthy subjects. Anal Bioanal Chem, 2009; 394(05): 1477–1484.
8. El Balkhi S, Trocello JM, Poupon J, et al. Relative exchangeable copper: a new highly sensitive and highly specific biomarker for Wilson's disease diagnosis. Clin Chim Acta, 2011; 412(23-24): 2254–2260.
9. El Balkhi S, Trocello JM, Poupon J, et al. Relative exchangeable copper: a new highly sensitive and highly specific biomarker for Wilson's disease diagnosis. Liver Int, 2012; 44(01): 192–200.
10. Poujois A, Trocello JM, Djebrani-Oussedik N, et al. Exchangeable copper: a reflection of the neurological severity in Wilson's disease. Eur J Neurol, 2017; 24(01): 154–160.
11. Guillaud O, Brunet AS, Mallet I, et al. Relative exchangeable copper: a valuable tool for the diagnosis of Wilson disease. Liver Int, 2018; 38(02): 350–357.
12. Mariño Z, Molera-Busoms C, Badenas C, et al. Benefits of using exchangeable copper and the ratio of exchangeable copper in a real-world cohort of patients with Wilson disease. J Inherit Metab Dis., 2023; 46(05): 982–991.
13. Ngwanou DH, Couchonnal E, Parant F, et al. Long-term urinary copper excretion and exchangeable copper in children with Wilson disease under chelation therapy. J Pediatr Gastroenterol Nutr, 2022; 75(04): e75–e80.
14. Jacquelet E, Poujois A, Pheulpin MC, et al. Adherence to treatment, a challenge even in treatable metabolic rare diseases: a cross sectional study of Wilson's disease. J Inherit Metab Dis., 2021; 44(06): 1481–1488.
15. Trocello JM, El Balkhi S, Woimant F, et al. Relative exchangeable copper: a promising tool for family screening in Wilson disease. Mov Disord, 2014; 29(04): 558–562.

16. Solovyev N, Ala A, Schilsky M, Mills C, Willis K, Harrington CF. Biomedical copper speciation in relation to Wilson's disease using strong anion exchange chromatography coupled to triple quadrupole inductively coupled plasma mass spectrometry. Anal Chim Acta, 2020; 1098: 27–36.
17. Del Castillo Busto ME, Cuello-Nunez S, Ward-Deitrich C, Morley T, Goenaga-Infante H. A fit-for-purpose copper speciation method for the determination of exchangeable copper relevant to Wilson's disease. Anal Bioanal Chem, 2022; 414(01): 561–573.
18. Barada K, El-Atrache M, El-Hajj II, Rida K, El-Hajjar J, Mahfoud Z, Usta J. Homozygous mutations in the conserved ATP hinge region of the Wilson disease gene: association with liver disease. J Clin Gastroenterol, 2010; 44: 432-439 [PMID: 20485189 DOI: 10.1097/MCG.0b013e3181ce5138]
19. Loudianos G, Dessi V, Lovicu M, Angius A, Figus A, Lilliu F, De Virgiliis S, Nurchi AM, Deplano A, Moi P, Pirastu M, Cao A. Molecular characterization of wilson disease in the Sardinian population--evidence of a founder effect. Hum Mutat, 1999; 14: 294-303 [PMID: 10502776]
20. Giagheddu A, Demelia L, Puggioni G, Nurchi AM, Contu L, Pirari G, Deplano A, Rachele MG. Epidemiologic study of hepatolenticular degeneration (Wilson's disease) in Sardinia (1902-1983). Acta Neurol Scand, 1985; 72: 43-55 [PMID: 3876678]
21. Gialluisi A, Incollu S, Pippucci T, Lepori MB, Zappu A, Loudianos G, Romeo G. The homozygosity index (HI) approach reveals high allele frequency for Wilson disease in the Sardinian population. Eur J Hum Genet, 2013; 21: 1308-1311 [PMID: 23486543 DOI: 10.1038/ejhg.2013.43]
22. Zappu A, Magli O, Lepori MB, Dessì V, Diana S, Incollu S, Kanavakis E, Nicolaidou P, Manolaki N, Fretzayas A, De Virgiliis S, Cao A, Loudianos G. High incidence and allelic homogeneity of Wilson disease in 2 isolated populations: a prerequisite for efficient disease prevention programs. J Pediatr Gastroenterol Nutr, 2008; 47: 334-338 [PMID:18728530 DOI:10.1097/MPG.0b013e318170 94f6].
23. Vrabelova S, Letocha O, Borsky M, Kozak L. Mutation analysis of the ATP7B gene and genotype/phenotype correlation in 227 patients with Wilson disease. Mol Genet Metab, 2005; 86: 277-285 [PMID: 15967699 DOI:10.1016/j.ymgme.2005.05.004].
24. Nicastro E, Loudianos G, Zancan L, D'Antiga L, Maggiore G, Marcellini M, Barbera C, Marazzi MG, Francavilla R, Pastore M, Vajro P, D'Ambrosi M, Vegnente A, Ranucci G, Iorio R. Genotypephenotype correlation in Italian children with Wilson's disease. J Hepatol, 2009; 50: 555-561 [PMID: 19118915 DOI: 10.1016/j.jhep.2008.09.020].
25. Lee BH, Kim JH, Lee SY, Jin HY, Kim KJ, Lee JJ, Park JY, Kim GH, Choi JH, Kim KM, Yoo HW. Distinct clinical courses according to presenting phenotypes and their correlations to ATP7B mutations in a large Wilson's disease cohort. Liver Int, 2011; 31: 831-839 [PMID: 21645214 DOI: 10.1111/j.1478-3231.2011.02503.x].
26. Ferenci P, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, Schilsky M, Cox D, Berr F. Diagnosis and phenotypic classification of Wilson disease. Liver Int, 2003; 23: 139-142 [PMID: 12955875 DOI: 10.1034/j.1600-0676.2003.00824.x].
27. Schilsky ML, Scheinberg IH, Sternlieb I. Liver transplantation for Wilson's disease: indications and outcome. Hepatology, 1994; 19: 583-587 [PMID: 8119682].
28. Walshe JM. Wilson's disease presenting with features of hepatic dysfunction: a clinical analysis of eighty-seven patients. Q J Med, 1989; 70: 253-263 [PMID: 2602537].
29. Scott J, Gollan JL, Samourian S, Sherlock S. Wilson's disease, presenting as chronic active hepatitis. Gastroenterology, 1978; 74: 645-651 [PMID: 75819].

30. Wiethoff H, Mohr I, Fichtner A, et al. Metallothionein: a game changer in histopathological diagnosis of Wilson disease. Histopathology, 2023; 83(06): 936–948.
31. Schilsky ML, Blank RR, Czaja MJ, et al. Hepatocellular copper toxicity and its attenuation by zinc. J Clin Invest 1989; 84(05): 1562–1568
32. Członkowska A, Rodo M, Wierzchowska-Ciok A, Smolinski L, Litwin T. Accuracy of the radioactive copper incorporation test in the diagnosis of Wilson disease. Liver Int 2018; 38(10): 1860–1866
33. Sandahl TD, Gormsen LC, Kjærgaard K, et al. The pathophysiology of Wilson's disease visualized: a human 64Cu PET study. Hepatology 2022; 75(06): 1461–1470
34. Espinós C, Ferenci P. Are the new genetic tools for diagnosis of Wilson disease helpful in clinical practice? JHEP Rep Innov Hepatol 2020; 2(04): 100114
35. Weiss KH, Thurik F, Gotthardt DN, et al; EUROWILSON Consortium. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. Clin Gastroenterol Hepatol 2013; 11(08): 1028–35.e1, 2
36. Munk DE, Lund Laursen T, Teicher Kirk F, et al. Effect of oral zinc regimens on human hepatic copper content: a randomized intervention study. Sci Rep 2022; 12(01): 14714
37. Kirk FT, Munk DE, Swenson ES, et al. Effects of trientine and penicillamine on intestinal copper uptake: a mechanistic 64 Cu PET/CT study in healthy humans. Hepatology 2024; 79(05): 1065–1074
38. Siegemund R, Lössner J, Günther K, Kühn HJ, Bachmann H. Mode of action of triethylenetetramine dihydrochloride on copper metabolism in Wilson's disease. Acta Neurol Scand 1991; 83(06): 364–366.