Evaluation of the Liver and Pancreas by 2D Shear Wave Elastography in Pediatric Wilson's Disease

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ABSTRACT

Background: *The primary aim of the study was to demonstrate parenchymal changes in the liver and pancreas related to copper accumulation using ultrasound in pediatric patients with Wilson's disease and secondly, to investigate the effectiveness of two-dimensional shear wave elastography in the diagnosis of involvement of these organs.*

Methods: *Patients with Wilson's disease (n = 25) who were treated and followed at our center were evaluated prospectively. In addition to routine clinical assessments, eye examination, laboratory analyses, and abdominal ultrasound imaging, all patients underwent tissue stiffness measurements from the liver and pancreas (head, body and tail) by two-dimensional shear wave elastography. The data obtained from the WD patients were compared with those of age- and sex-matched healthy controls (n = 37).*

Results: *Liver elastography measurements showed significantly increased tissue stiffness in the patient group than in control subjects (P < .001). While there was no significant difference between the groups in the tissue thickness of pancreatic head, body, and tail, tissue stiffness was significantly reduced in the patient group (P < .001). Disease duration was significantly associated and moderately correlated with liver tissue stiffness (r = 0.417, P = .038) but not significantly associated with pancreatic tissue stiffness.*

Conclusion: *In the early stages of Wilson's disease, parenchymal changes occur in the liver and pancreas, which cannot be detected by conventional ultrasonography imaging but may be demonstrated by two-dimensional shear wave elastography. Ultrasound elastography is an easy to use, non-invasive, and promising method that provides numerical data on the early changes in tissue stiffness, allowing for objective monitoring of Wilson's disease patients who require lifelong follow-up.*

Keywords: *Children, liver, pancreas, shear wave elastography, Wilson disease*

INTRODUCTION

Wilson's disease (WD) is a metabolic disorder resulting from defective biliary excretion of copper, which is inherited in an autosomal recessive pattern. Wilson's disease is a rare condition with a reported incidence of 1/30 000 and a gene frequency of 1/90-150.[1] The disease most often manifests itself with signs of hepatic and neuropsychiatric involvement, but when the copper storage capacity of the liver is exceeded, copper that is released into the bloodstream from damaged hepatocytes accumulates in other organs (e.g., eyes, kidneys, bone, heart, pancreas, and parathyroid gland), leading to organ dysfunction.[2] Wilson's disease mostly becomes symptomatic in childhood and young adulthood, and it is characterized by predominantly hepatic symptoms in 58% of patients.[3] Diagnosis is based on clinical scoring systems in patients with WD, and a liver biopsy is performed if the clinical signs and non-invasive tests do not allow a definite diagnosis or if there is a suspicion of other liver disorders.[1] The earliest histopathologic abnormalities detected in the liver include mild steatosis (macrovesicular and microvesicular) and focal hepatocellular necrosis. Fibrosis and subsequently cirrhosis develop following progressive parenchymal damage.[1] However, since repeat biopsies are not performed during the follow-up after the diagnosis, there is very little information on the progression of hepatic fibrosis, and hepatic function gradually deteriorates in 12% of patients receiving treatment.[3] Since appropriate treatment improves liver function and long-term outcomes in patients with WD, monitoring hepatic fibrosis is clinically important.[4]

Elastography is an imaging method that enables the assessment of tissue biomechanical properties qualitatively and quantitatively by means of ultrasound (US), and it is used to obtain elasticity values of the tissues in meter/second (m/s) or kilopascal (kPa).[5] For this purpose, non-imaging elastography technique (transient

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elastography) and combined imaging techniques (point shear wave and two-dimensional shear wave elastography (2D SWE)) are used.[5] Although liver biopsy is the gold standard, these techniques have been validated as accurate non-invasive diagnostic tools for liver fibrosis.[5-7] However, due to the rarity of the disease, these techniques have not been extensively studied for patients with WD, and there are only a few studies using different techniques.[3,4,8,9]

Pancreatic cell damage and secondary fat infiltration due to cytotoxic effects of iron overload in conditions such as idiopathic hemochromatosis and thalassemia have been demonstrated in studies.[10] However, few studies have examined pancreatic accumulation of copper, which is also a transition metal ion like iron and has similar cytotoxic effects because it does not produce clinically significant pancreatic symptoms in patients with WD.[2]

The aim of this study was to determine the parenchymal changes associated with copper accumulation in the liver and pancreas using US in pediatric patients with WD in comparison to healthy children and to investigate the effectiveness of 2D-SWE for the detection of hepatic and pancreatic involvement.

MATERIALS AND METHODS

For this single-center study, Institutional Clinical Research Ethics Committee (No. 1406201989/39) approval was obtained prior to the study. A total of 25 WD patients and 37 healthy children who were treated, followed, or consulted at our clinic between June 2018 and April 2019 were included in the study.

Study Sample

Patients younger than 18 years of age with WD diagnosed according to the Ferenci scoring system who were treated and followed at our pediatric gastroenterology clinic between June 2018 and April 2019 were included in this study.[11] Patients who refused to participate in the study, and patients who participated but did not comply with breath-holding instructions were excluded from the study. Written informed consent was obtained from all patients or their parents. Clinical evaluation, eye examination, laboratory analyses (hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyltransferase, total protein, albumin, total/direct bilirubin, prothrombin time (PT), activated partial thromboplastin time), abdominal US imaging, and 2D-SWE were performed for study subjects. The body weight and height of the patients were measured to calculate the body mass index (BMI). The stage of hepatic manifestations was categorized according to a scoring system previously described by Karlas et al[4] as follows:

- Category 1: normal liver US morphology and no clinical or biochemical signs of liver manifestation.
- Category 2: normal liver US morphology and elevated serum aminotransferase levels (ALT or AST).
- Category 3: sonographic abnormalities of liver morphology (i.e., heterogeneous/increased parenchymal echogenicity) without signs of liver cirrhosis.
- Category 4: sonographic (i.e., portal hypertension findings, coarse parenchymal nodularity, splenomegaly, caudate lobe hypertrophy, irregular liver margins) and clinical (e.g., thrombocytopenia, gastric or esophageal varices, thrombocytopenia, splenomegaly) signs of liver cirrhosis with compensated liver function (Child–Pugh class A)
- Category 5: liver cirrhosis with decompensated liver function (Child–Pugh Classes B and C).

- The control group consisted of age- and sex-matched healthy children without any chronic or systemic condition, who underwent abdominal US imaging at the department of radiology for reasons other than pancreatic or hepatic diseases. The body weight and height of the control subjects were measured to obtain the body mass index. Ultrasound assessment and 2D-SWE measurements were also performed for the control subjects.

Main Points

- *In the early stages of Wilson's disease, parenchymal changes occur in the liver and pancreas, which can be demonstrated by two-dimensional shear wave elastography.*
- *Two-dimensional shear wave elastography showed significantly reduced pancreas tissue stiffness in Wilson's disease.*

Conventional B-Mode Ultrasonography and Two-Dimensional Shear Wave Elastography Evaluations

All US examinations were conducted by a radiologist with more than 5 years of experience in the field of abdominal radiology and US imaging. For both groups, imaging studies were performed in 2 parts after 3 hours of fasting: 2D-SWE and conventional B-mode US. Evaluations were

done using a LOGIQ E9 ([LE]; GE Healthcare, Wauwatosa, WI) device with a convex, wide-band abdominal US probe (6C1, 1.5-6 MHz). Before imaging, patients were placed in a semi-supine position. First, the US probe was placed over the right intercostal region to visualize the liver. Conventional US findings were evaluated on the B-mode. Two-dimensional shear wave elastography measurements were obtained using the elastogram display mode (Figure 1). Two-dimensional elastography color maps were obtained by placing a region of interest (ROI) box in the subcapsular area of the hepatic parenchyma, on a single breath-hold. Care was exercised to avoid placement of the ROI box on the liver capsule, biliary tree, and vascular structures. Then, SWE values in meter (m)/second (s) were obtained with a circular ROI (5 × 5 mm) placed on 2D color elastography maps in static mode. This procedure was repeated 5 times consecutively, and average values were calculated. Next, the US probe was placed over the epigastric region to visualize the entire pancreas. On the B-mode image, parenchymal thickness was measured for the pancreatic head, body, and tail segments separately. Two-dimensional shear wave elastography measurements were repeated 5 times for pancreatic head, body, and tail individually as described for the liver, and average values were obtained. Care was taken to avoid placement of the elastography ROI on the bile ducts or large vessels.

Statistical Analysis

Statistical analysis was performed to compare the WD group and the healthy control group. Descriptive statistics for categorical variables were presented as numbers (n) and percentages. The normal distribution of the results was checked by the Kolmogorov–Smirnov test. The liver and pancreas measurements and clinical parameters were compared between patients with WD and healthy control using the Mann–Whitney *U*-test or chi-square test. All US and elastography measurements were summarized as median with interquartile ranges. The Friedman test was used to compare 2D-SWE measurements among 3 different segments of the pancreas. The Spearman's correlation analysis was used to determine correlations among liver and global pancreatic 2D-SWE measurements and disease duration. Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) program, version 23.0 (IBM Corp.; Armonk, NY, USA), and the significance level was set at .05.

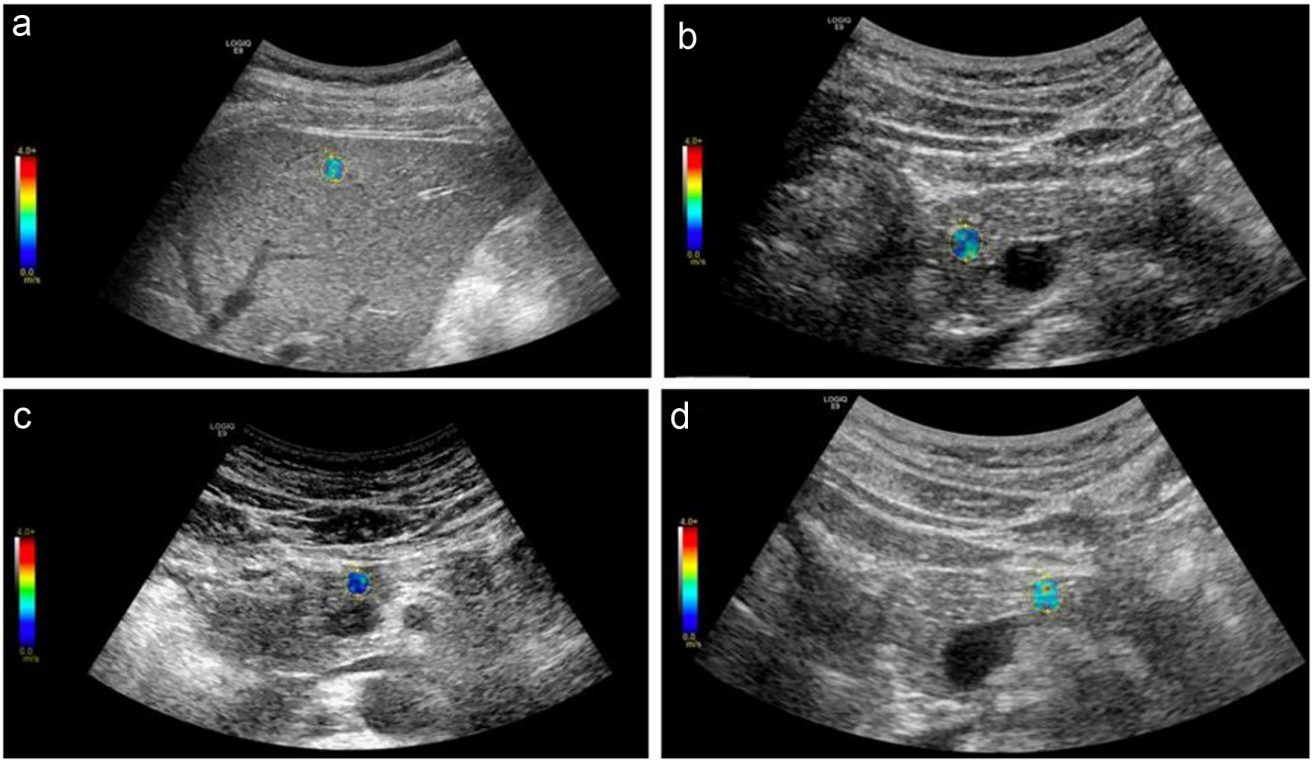

Figure 1. Measurements obtained from the liver (a) and head (b), body (c), and tail (d) segments of the pancreas.

RESULTS

Among 30 patients eligible for this study, 3 patients did not agree to participate in the study between the specified dates and 2 patients were excluded due to non-compliance with breath-holding instructions during the evaluation. Ultimately, 25 patients with WD who were willing to participate in the study and showed compliance to breath-holding instructions were evaluated prospectively. Hepatic manifestation stages and data distribution of the study groups are summarized in Table 1 for all patients. In the majority of patients [n = 19, (76%)], the hepatic manifestation stage was category 2 where only enzyme elevation was observed. In addition to liver sonomorphology and laboratory findings of WD, four patients had neurologic signs (tremor, dysarthria, ataxia, and behavioral disorder) and 2 patients had ophthalmic signs (Kayser-Fleischer ring).

The demographic characteristics of the patient and control groups and the laboratory analysis results of the patient group are summarized in Table 2. There was no significant difference between the groups in terms of sex, age, body weight, or height. However, the BMI and standardized body mass index (BMI-SDS) were significantly different between the groups, with significantly lower values found for patients with WD (Table 2).

The thickness and tissue stiffness (TS) measurements of the pancreatic head, body, and tail and TS measurements of the hepatic parenchyma are shown in Table 3. The liver tissue measurements showed significantly greater TS values in the WD group compared to the control group ($P < .001$). While pancreatic tissue thickness as measured by conventional US did not differ significantly between the groups, SWE measurements of the pancreatic head, body, and tail demonstrated significantly lower TS values in the WD group (Table 3). Moreover, TS measurements were not significantly different among 3 pancreatic regions in the WD group ($\chi^2 = 0.138$, $P = .933$).

A correlation analysis showed a moderately significant correlation between follow-up duration (months) and hepatic TS measurements in the WD group ($r = 0.417$, $P = .038$). However, correlation analyses did not reveal a correlation or significant association between the global pancreatic TS measurement (average of pancreatic measurements) ($r = 0.331$, $P = .203$) and follow-up duration ($r = 0.365$, $P = .073$).

DISCUSSION

Elastography can serve as a non-invasive method for early diagnosis of the pre-cirrhotic stage of hepatic fibrosis before the onset of clinical manifestations of cirrhosis. In WD, as with other diseases causing chronic liver damage, the liver becomes fibrotic and fibrosis eventually progresses to cirrhosis. Therefore, the prognosis is directly related to the development and progression of fibrosis, but there are few studies that demonstrated fibrosis progression using elastography.[12] In a study by Karlas et al[4] in adult WD patients, transient elastography (TE) showed a gradual increase in the TS values among different stages of hepatic manifestation and could significantly discriminate cirrhosis (categories 4 and 5) at a cutoff value of 6.1 kPa. Similarly, in a study by Hwang et al[3] involving patients with WD, increased liver stiffness values in parallel with the clinical stage of hepatic manifestation were demonstrated using TE and 2D-SWE.[3] However, in both studies, no significant difference was observed in liver stiffness between patients with elevated aminotransferase levels only (category 2) and patients with aminotransferase levels in the normal range (category 1). Despite that, our patient group consisted mainly of asymptomatic patients with biochemical abnormalities only, and significantly increased liver stiffness was found in the study patients compared

Table 1. Hepatic Manifestation Stages and Patient Distributions of Wilson's Disease

Hepatic Manifestation Stage	Category 1 Not Involved	Category 2 Only Biochemical	Category 3 Altered Liver Morphology	Category 4 Compensated Cirrhosis	Category 5 Decompensated Cirrhosis
Aminotransferases	≤ULN	>ULN	-	-	-
Clinic symptoms of hepatic manifestation	None	None	None	Child-Pugh class A	Child-Pugh class B, C
Liver sonomorphology	Normal	Normal	For example, heterogeneous parenchymal echogenicity	For example, coarse parenchymal nodularity, presence of portal hypertension findings	
n (%)	3 (12%)	19 (76%)	3 (12%)	0	0

ULN, upper limit of normal value.

Table 2. Demographic Data of the Wilson's Disease and Healthy Control Groups, and the Laboratory Analysis Results of the Wilson's Disease Group

Mean ± SD (Min-Max)	Wilson's Disease Group, (n = 25)	Healthy Control Group, (n = 37)	*P*
Female, n (%)	9 (36%)	17 (45.9%)	.436
Male, n (%)	16 (64%)	20 (54.1%)	
Age, years	10.72 ± 2.62 (6 to 16)	9.83 ± 3.42 (5 to 16)	.345
Height, cm	140.08 ± 17.16 (110 to 176)	136.78 ± 19 (105 to 168)	.580
Body weight, kg	33.76 ± 13.72 (19 to 75)	35.87 ± 13.68 (17 to 60)	.446
BMI (kg/m^2)	16.43 ± 2.72 (12.60 to 24.20)	18.34 ± 2.86 (14.31 to 24.56)	.012
BMI-SDS	−0.90 ± 0.92 (−2.92 to 0.70)	0.16 ± 0.90 (−1.66 to 2.35)	<.001
Disease duration	41.24 ± 23.45 (15 to 96)	-	
AST	103.76 ± 71.71 (25 to 330)	-	
ALT	90.44 ± 83.65 (20 to 408)	-	
Albumin	4.05 ± 0.3 (3.30 to 4.60)	-	
ALP	244.56 ± 70.38 (120 to 448)	-	
GGT	45.32 ± 47.50 (14 to 260)	-	
PT	12.74 ± 1.19 (10.8 to 15)	-	
aPTT	28.82 ± 3.58 (21 to 35.2)	-	
PLT count (×10^3)	210.52 ± 87.374 (75 to 390)	-	

BMI, body mass index; SD, standard deviation; BMI-SDS, standardized body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase; PT, prothrombin time; aPTT, activated partial thromboplastin time; PLT, platelet.

Table 3. Comparison of 2D-SWE and Conventional US measurements Between Pediatric Patients with Wilson's Disease and Healthy Control Group

Median (IQR)	Wilson's Disease Group (n = 25)	Healthy Control Group (n = 37)	*P*
Liver			
2D-SWE (m/s)	1.06 (0.91-1.32)	0.89 (0.80-0.98)	<.001
Pancreatic head			
2D-SWE (m/s)	1.16 (1.07-1.29)	1.31 (1.23-1.39)	<.001
Diameter (mm)	13 (12.5-15)	13 (11 –15)	.184
Pancreatic body			
2D-SWE (m/s)	1.16 (1.1-1.27)	1.3 (1.2-1.36)	<.001
Diameter (mm)	12 (11.7-13.5)	12 (10-14.5)	.617
Pancreatic tail			
2D-SWE (m/s)	1.1 (1.08-1.23)	1.3 (1.22-1.35)	<.001
Diameter (mm)	12 (10.5-14.8)	13 (11-14)	.834

IQR, interquartile range; 2D-SWE, two-dimensional shear wave elastography.

to the healthy controls. In another study, Stefanescu et al[9] examined whether intrahepatic copper accumulation could have an effect on increased liver stiffness in addition to parenchymal fibrosis in adult patients with WD. In that study, they showed a reduction in liver stiffness in parallel with an increase in urinary copper excretion during follow-up but reported that the reduction in liver stiffness was not statistically significant possibly due to small sample size (9 patients). Copper accumulation in the liver starting from the early stages of WD could be another reason for increased liver stiffness observed in our study group compared to the control group. In addition, there was a

moderately significant correlation between liver stiffness measurements and follow-up duration.

Copper is found in a variety of cells and tissues in the body, with the highest concentrations in the liver and brain. Thus, studies on copper metabolism disorder have often focused on presentations associated with liver and brain involvement. However, as with other heavy metals such as iron, copper can also accumulate in a number of organs and lead to diseases through various mechanisms. In the case of rarely occurring WD, pancreatic involvement has been overshadowed by other organ involvements and not extensively studied. In a study of patients with thalassemia major with pancreatic involvement induced by iron, a heavy metal like copper, iron overload, and secondary fatty infiltration of the pancreas were reported.[10] Fatty infiltration of the pancreas was explained by the progressive replacement of the pancreatic parenchyma with adipose tissue following the death of pancreatic cells due to cytotoxic effects of iron. In that study, it was suggested that exocrine glands diffusely distributed in the pancreas are involved mainly in the early stages of the disease, and fatty replacement of the pancreatic parenchyma follows iron deposition. In the later stages of the disease, fatty infiltration and iron overload progressively exhibit a heterogeneous distribution, with involvement of the endocrine pancreas. In the current study, 3 different regions of the pancreas were evaluated individually, and while conventional US findings did not demonstrate a significant difference between the groups, 2D-SWE showed significantly reduced TS in the patient group. Additionally, no significant difference was found in tissue stiffness among 3 pancreatic regions, demonstrating diffuse involvement of the pancreas. We consider that copper, which is a heavy metal like iron, accumulates in the pancreas, primarily in the exocrine tissue, causing tissue damage via a similar mechanism. In a study on cystic fibrosis, another disease that involves pancreas, it was shown that destruction and atrophy of the exocrine pancreas start from early childhood, and pancreatic tissue is replaced first by adipose tissue in the early stage and by fibrous tissue in the later stages.[13] Diffuse involvement of the pancreas and significantly reduced TS in the pancreatic head, body, and tail were shown by 2D-SWE in patients with cystic fibrosis when compared with healthy controls in studies by Pfahler et al and Pişkin et al.[14,15] These studies have also demonstrated diffuse involvement of the pancreas during exocrine pancreas damage, and the diffuse involvement of the pancreas as observed in the current study indicates predominant exocrine pancreatic involvement due to copper accumulation. Malnutrition and growth retardation are important concerns in WD. While there was no significant difference between WD and control groups in terms of height and body weight distribution, BMI and BMI-SDS values were significantly lower in the WD group, which may be related to the exocrine pancreas damage. In contrast to hepatic TS, a significant association was not found between the disease duration and pancreatic tissue stiffness in our study. This can be explained by the young age of our patient population and the predominance of copper accumulation in the liver in WD. We believe that a study conducted in the adult age group may provide additional information on this issue.

Our study has a number of limitations. First, hepatic manifestations were assessed using previously described clinical scoring systems, and pathologically proven severity of fibrosis could not be evaluated. Histological grading is the gold standard in determining the severity of fibrosis, and biopsy was not performed simultaneously in our study for patients with regular follow-up visits in order to avoid biopsy-related complications. Secondly, pancreatic involvement was not confirmed histologically for. Thirdly, the WD patients in the study group have been followed for a long term and had a relatively stable course of liver disease. It is known that successful treatment of WD may improve the course of liver disease and slow the progression of fibrosis.[16] Therefore, liver stiffness measurements may have been biased. Lastly, the study group lacked patients with compensated or decompensated cirrhosis (categories 4 and 5), which represents an important limitation.

In conclusion, this study demonstrated parenchymal changes in the liver and pancreas that cannot be detected by conventional US imaging but may be demonstrated by US elastography in stable patients with WD. No other study was identified in the literature that examined pancreatic involvement in patients with Wilson's disease using elastography, and there is a need for controlled studies in larger patient series to determine the distribution of disease severity using pancreas-specific tests. Lifelong follow-up is required for patients with WD to monitor disease progression and response to treatment and to identify potential clinical complications. Ultrasound elastography allows for objective monitoring of the progression of fibrosis over time by providing numerical data on the changes in TS. Ultrasound elastography offers a non-invasive and promising method to monitor this chronic disease and demonstrate associated changes in the tissues.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee.

Informed Consent: Informed consent was obtained from legal guardians to participate.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept – G.T.; Design – S.Y.; Supervision – S.S.; Resources – C.O.; Materials – F.C.P.; Data Collection and/or Processing – S.B.; Analysis and/or Interpretation – C.O.; Literature Search – S.Y.; Writing Manuscript – S.Y., F.C.P.; Critical Review – G.T.

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