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Review paper

The importance of elastography in hepatological diagnostics in children

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Abstract

About 30 years have passed since elastography was first used, with the greatest popularity in the last 10 years. The use of this diagnostic method is particularly important in patients with liver disease. FibroScan shows higher sensitivity in assessing the degree of organ steatosis and fibrosis compared to ultrasound. The noninvasive nature and ease of performance make it possible to perform the test in most pediatric patients. Owing to the correlation of the results with the histopathological evaluation, elastography replaces liver biopsy in many cases. Given the epidemic of childhood obesity observed in recent years, FibroScan testing appears to be increasingly necessary.

Key words: obesity, fibrosis, steatosis, liver disease, FibroScan.

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Introduction

Elastography as a method to study tissue stiffness was first used in the early 1990s (1991) by Ophir *et al*. at the University of Texas Medical School, Houston. Initial measurements were performed on phantoms and animal tissues [1]. Elastography provides a quantitative non-invasive assessment of the extent of liver damage, is used to assess fibrosis of the liver parenchyma, and utilizes tissue elasticity, which is defined as the ability to resist deformation or restore shape after removal of an externally applied force [2].

Types of measurements and evaluation parameters

The most widely used method in practice is transient elastography (TE), which is available on the FibroScan device to assess the degree of organ steatosis and fibrosis. This method involves measuring the speed of propagation of a mechanical impulse (elastic wave) using ultrasound. A special head applied to the skin of the subject (right side) generates a mechanical impulse that penetrates the skin toward the liver. At the same time, the ultrasound transducer performs a series of measurements of the propagation of the mechanical impulse. The speed of wave propagation increases with the degree of fibrosis in the liver.

In the process of tissue fibrosis, extracellular elements, such as collagen and elastin, play a significant role; their quantity in the liver increases with the duration of the disease. Elastography results are expressed in kPa (stress/tissue strain ratio) or transverse wave velocity in meters per second (m/s) [2-4]. FibroScan also assesses steatosis using the Controlled Attenuation Parameter (CAP), which is expressed in decibels per meter (dB/m) [4].

Advantages of elastography

When choosing the type of test method, it is important that it is easy to perform, reproducible, has high sensitivity and specificity, and has an optimal price. All of these features apply to elastography.

The non-invasiveness and absence of ionizing radiation in the application of this method should be emphasized. In a group of children, age, and weight influence the measurement results; other factors influencing the result value include exertion, comorbidities, respiratory phases, and whether the patient is fasting or after a meal [2, 5].

Elastography in children

It is suggested that the examination parameters be adjusted more to anthropometric measurements rather than to age due to the possibility of being underweight or overweight [5]. In infants, the position of the liver is often about 3-3.5 cm below the lower edge of the rib margin, so attention should be paid to where the probe is applied [5]. Some data show differences in liver elasticity according to age, and gender differences have also been detected in adults [5].

Most researchers recommend taking about 10 measurements during the study, the average of which is the final result. It is also important that the measurement values are close to each other; the difference between the extreme values should be less than 30% [6]. In the Mjelle study, which investigated the use of elastography in a group of healthy children, no significant difference was found between performing 3 and 10 measurements. Additionally, the duration of the examination is of great importance to the child [7].

It should be noted that patient movement during the examination significantly interferes with obtaining reliable results. This limitation is important in the pediatric group [8]. There is a lack of data evaluating the difference in measurements in children for breath holding and free breathing. It is known that stopping breathing for the duration of the measurement has a positive effect on the repeatability of the results, but this is only possible in a group of children over the age of 5 [5]. In adults, it has been found that measurements from the right lobe of the liver are more reliable than those from the left lobe of the liver; the site of measurement in children has not been clearly established [5].

Elastography is an examination method that has grown in popularity in recent years. One of its main advantages, especially in the pediatric group, is its non-invasive nature. A special probe was designed for young and slim patients to facilitate the examination [9].

Correlation of results with other methods

Interest in the use of elastography in pediatrics has increased in the last decade, with most publications dating from this period. In clinical practice, it is mainly used to assess liver fibrosis, but it offers the possibility of measuring the tissue stiffness of other organs: kidney, spleen, bladder, pancreas, thyroid, lymphoid tissue, or brain [2]. The evaluation of the role of this diagnostic method in children requires further research to clearly assess the indications and interpretations of the results obtained.

Based on data to date, it is already known that liver elastography findings correlate with histopathological examination in assessing the degree of liver fibrosis. This applies to a group of patients with cystic fibrosis, metabolic fatty liver disease, short bowel syndrome, Wilson's disease, polycystic kidney disease, portal hypertension, biliary atresia after the Kasai procedure, and those who have undergone liver transplantation [2]. Guidelines prepared by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) and the World Federation for Ultrasound in Medicine and Biology (WFUMB) for adult patients cannot be applied to children. Therefore, further research is needed to develop appropriate algorithms [5].

Assessment of fibrosis

In a study by Lee *et al.* conducted among patients over 10 years of age and young adults (with an average age of 13 years), all enrolled patients had undergone a liver biopsy within the last 12 months. Two types of probes were used for elastographic measurements: S for patients with waist circumferences < 75 cm and M for patients with waist circumferences > 75 cm. This study determined the values obtained during elastography, which will serve to differentiate the degree of fibrosis F3-F4 (advanced liver fibrosis) from F4 (cirrhosis). The METAVIR scale was used in this study. This analysis confirmed liver stiffness measurements (LSM) cut-off points in children and young adults of 8.6 kPa for F3-F4 subjects and 11.5 kPa for F4 [3]. Knowledge of these values facilitates the classification of patients into high-risk fibrosis groups, the establishment of an appropriate diagnostic process, and patient monitoring. With knowledge of the cut-off points for the degree of liver fibrosis, it is possible to prepare guidelines to help identify children with advanced fibrosis [3].

Hepatitis affects the stiffness of the liver. In a study by Raizner *et al.* of 154 patients aged between three weeks and 24 years, it was found that in patients with F0-F2, the number of patients with LSM > 8.6 kPa increased with increasing alanine amino-transferase (ALT) activity. In the group of patients with F3-F4, no correlation between ALT and LSM was observed. The results of the above study dictate caution in the as-

sessment of LSM in a group of children with abnormal aminotransferase activity [10].

In a group of infants with biliary atresia where children are already eligible for Kasai hepatoportoenterostomy in the first weeks of life, elastography may become an effective tool to facilitate the assessment of liver fibrosis both preoperatively and postoperatively. The introduction of pediatric probes (S1, S2) has made it possible to use elastography in infants, but the use of this method still needs further dissemination and observation [8, 11]. Kim *et al*. analyzed the elastography results of 100 patients with biliary atresia after Kasai surgery without liver transplantation. Patients were divided into a group of children with chest circumferences < 45 cm and > 45 cm. They underwent elastography and laboratory tests – blood count and assessment of aspartate aminotransferase activity – and APRI (aspartate aminotransferase to platelet ratio – AST/PLT) was calculated [11]. The authors found a correlation between the use of probes of different sizes, S1, S2, and M, and the APRI index. In a group of children with chest circumferences < 45 cm, the S1 probe seems to be the most suitable; in a group of children with chest circumferences > 45 cm, if the S probe is unavailable, the M probe can be used [11]. Li *et al*. conducted a meta-analysis of the use of elastography in patients with biliary atresia, which included 490 patients (7 articles). The results of this work indicated the high diagnostic value of elastography in the group of patients with biliary atresia; its sensitivity and specificity were 90%. The use of measurement of the degree of fibrosis as an additional tool in the diagnostic process, in addition to abdominal ultrasound, should facilitate and, above all, accelerate the diagnosis of patients with biliary atresia [8]. Some of the selected studies compared the use of elastography and magnetic resonance cholangiopancreatography (MRCP). The results indicated higher diagnostic accuracy of MRCP; hence, further observations should be made on the use of elastography [4, 8].

Evaluation of other parameters

Liver disease in children often requires a number of diagnostic tests, including laboratory tests, microbiological tests and imaging studies. Liver biopsy is an invasive method that remains the gold standard for many diseases. Due to possible complications, a search is underway for a method that can be substituted for biopsy in certain situations or reduce the frequency of biopsy [6]. Disease processes in the liver often cause liver fibrosis and contribute to higher mortality rates in these patients. The identification of individuals with fibrosis and steatosis can contribute to the earlier initiation of treatment, as children with liver disease often remain asymptomatic for long periods of time [6].

A report by the World Health Organization indicates that overweight and obesity is diagnosed in Poland in one-third of children aged 7-9 years, the 8th place among the surveyed countries in Europe. The proportion of overweight and obese children increases with age. Most obese pediatric patients also have this problem in adulthood. Obesity is a multifactorial condition. A proven, important factor in the prevalence of obesity in children is a high body mass index (BMI) in the mother [12]. In an analysis carried out by a team of researchers from Łódź (Poland), factors that increased the risk of overweight or obesity in children included, in addition to the mother's BMI, male gender, snacking between meals, low economic status and the time of the child's wake-up call (on non-school days, overweight children got up earlier) [12]. Abnormal body weight contributes to altered liver cohesiveness and steatosis.

Metabolic dysfunction associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease in adolescents and adults. Epidemiological data indicate the prevalence of metabolic steatohepatitis in 3-10% of children. MASLD is more common in children over 10 years of age [13]. There is a lack of epidemiological data on its prevalence among younger children [4, 14]. Zeng *et al*. conducted an observational study of 848 children under the age of 8 with steatohepatitis and with steatohepatitis and obesity. The findings indicated a significant effect of obesity on the development of metabolic steatohepatitis in preadolescent children. In obese patients, the incidence of MASLD increased 6.5-fold between 5 and 8 years of age. Such a significant increase in a short period should draw our attention to the need for proper nutritional habits and maintaining an appropriate body weight from a young age [14]. In the diagnosis of MASLD, the gold standard for diagnosis is a liver biopsy. Due to the invasive nature of the test, the diagnosis is often made on the basis of aminotransferase activity and ultrasound imaging of the liver [13].

Więckowski *et al*. assessed the prevalence of hepatic steatosis and fibrosis in obese and normal-weight patients. The study showed significant differences in CAP values describing the amount of steatosis, while the degree of fibrosis did not differ significantly. The patients studied showed no abnormalities on abdominal ultrasonography, and aminotransferase activity was normal. The authors found that the use of an additional diagnostic tool, such as FibroScan, contributed to an earlier diagnosis of steatosis in 64% of obese

children, and that the degree of steatosis and fibrosis was proportional to the degree of obesity [15].

Few pediatric studies have compared measurements of liver stiffness (LSM) and degree of steatosis expressed as the CAP value with histopathological findings obtained by liver biopsy. Chaidez *et al*. evaluated the role of the FibroScan-aspartate aminotransferase score (FAST) in predicting the severity of liver disease in children with MASLD. Eligible patients were divided into a group with MASLD and a group with other diseases (autoimmune hepatitis, Wilson's disease, cystic fibrosis, primary sclerosing cholangitis, and portal hypertension) and without MASLD. The analysis showed significant correlations between the severity of fibrosis and steatosis as determined by FibroScan and histopathological examination in patients without MASLD. The FAST index satisfactorily differentiated the severity of liver disease, and correlated statistically significantly with LSM and CAP measured by FibroScan and AST activity. CAP has been shown to have the ability to differentiate the severity of steatosis, and a CAP value > 259 dB/m has a very high sensitivity (94%) and specificity (91%) in assessing the severity of steatosis. In the authors' opinion, studies on a larger number of patients are needed to determine the values for LSM, CAP, and FAST to assess the degree of fibrosis, steatosis, and progression of liver disease [16].

Jayasekera cited studies showing a correlation of CAP and LSM with common markers of steatosis and fibrosis, such as AST, ALT, and APRI activity [4].

In children with MASLD, tests to assess aminotransferase activity and liver imaging by elastography or MRI proton density fat fraction (MRI-PDFF) are indicated as a first diagnostic step, followed by consideration of indications for possible biopsy [4].

In addition to the diseases described in detail above, the use of elastography in pediatrics can also be used for children with chronic liver diseases, such as cystic fibrosis, metabolic liver disease, Gaucher's disease, Wilson's disease, a-1-antitrypsin deficiency, glycogen storage disease, and congenital heart defects after cardiac surgery correction [5]. Patients with congenital heart disease, for example, after a Fontan operation, may develop progressive liver disease; the use of elastography for the early detection of fibrosis allows rapid cardiac intervention and a halt to this process [5].

FibroScan should be an additional tool for liver assessment. Its availability should be widespread because of the large groups of patients, especially those with elevated aminotransferase activity, in whom the incorporation of preventive or therapeutic measures will be possible at the stage of reversible changes. This examination can show changes not yet visible on abdominal ultrasound, owing to the non-invasive nature of the examination; it can be repeated, and the patient can be regularly monitored. Patient monitoring is particularly important in the case of progressive diseases, so that appropriate therapeutic decisions, e.g., regarding the patient's eligibility for transplantation, can be made early. In addition, elastography can be used to evaluate an organ that has already been transplanted [5, 6]. FibroScan, due to its non-invasive nature, is helpful in assessing the impact of weight reduction on the degree of steatosis and fibrosis [12, 17]. This safe and radiation-free imaging method should be subject to further dissemination to pediatric patients. The development of standards for children with obesity and MASLD is particularly important given the increasing number of children with this problem [4].

Summary

The use of elastography in pediatrics requires further dissemination, evaluation of clear indications, and interpretation of the results obtained. Its non-invasive nature and few contraindications should be incentives to perform it more often. FibroScan results correlate with those obtained by liver biopsy, often allowing the biopsy to be waived. In the case of children, this is particularly important because of the need to anesthetize the patient for such an invasive diagnostic procedure.

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