Endocrinology

‘Tsunami’ of new NAFLD/NASH cases requires better management tools

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Two-thirds of patients with diabetes and/or obesity may have nonalcoholic fatty liver disease, or NAFLD, and just as many may have nonalcoholic steatohepatitis, or NASH, recent data indicate.

Despite these alarming numbers, clinicians and researchers are facing difficulties with outdated diagnostic tools, addressing patient compliance issues, and the lack of long-term controlled trials to determine the safety and efficacy of potentially useful pharmacotherapeutics.

“Physicians need to be aware that obesity and diabetes are the two most common predisposing factors to fatty liver,” Kenneth Cusi, MD, FACP, FACE, professor of medicine and chief of the division of endocrinology, diabetes and metabolism at the University of Florida at Gainesville, told Endocrine Today.

According to Kenneth Cusi, MD, FACP, FACE, obesity and diabetes are the most common factors that predispose people to fatty liver disease.

Photo by: Ale Palma

Additionally, Stephen A. Harrison, MD, an associate editor for Hepatology and professor of medicine at the Uniformed Services University of the Health Sciences, said almost one in two middle-aged adults have fatty liver disease in at least one recent prospective study.

"As an associate editor for Hepatology, I can attest to the rising interest in this field from an academic perspective, as the number of papers submitted for publication appears to be increasing significantly," Harrison told Endocrine Today. "This disease is being recognized at the GI level, and maybe it's starting to be recognized on the endocrine level and primary care level, but it's clearly not recognized at the lay person level."

Endocrine Today discussed the data and current trends, as well as practice barriers and their implications, with endocrinologists, gastroenterologists and hepatologists at the forefront of this increasing problem.

**Diagnosis of NAFLD/NASH**

Liver biopsy is the gold standard for diagnosing fatty liver disease in children and adults. Cusi said there are three situations in which a liver biopsy should be considered:

"If a) the liver enzymes are very high, or three times above the upper limit of normal (this would allow you to see the severity of the disease and decide upon treatment); b) the biopsy is going to help establish a diagnosis and move toward a given pharmacological treatment; or c) you are related to an academic center that is doing research in this area where they can offer new treatments," he said.

Screening for NAFLD is not recommended in all populations, though. According to practice guidelines published in *Hepatology* by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association, screening for NAFLD in adults attending primary care clinics or in high-risk groups attending diabetes or obesity clinics is not advised. This is due to uncertainties surrounding diagnostic tests and treatment options. This guideline also notes a lack of knowledge surrounding the long-term benefits and cost-effectiveness of screening.

Although liver biopsy is recognized by many experts as the paragon of diagnosis, radiographic imaging techniques (i.e., transient elastography, acoustic radiation force impulse elastography, MRI), apoptosis marker tests, and scoring systems (i.e., the FibroTest, Fibrometer, NAFLD fibrosis score, Fib-4, APRI, BARD, ELF, AST/ALT ratio) are other tools that are becoming more popular.

According to researchers, however, techniques such as ultrasound, MRI, and spectroscopy are not as effective as liver biopsy. Ultrasound measures fat but does not indicate whether there is inflammation, and MRI and spectroscopy are limited to research settings.

**A ‘silent killer’**

Although the guidelines are clear regarding diagnosing adults, they state that a lack of evidence does not allow a formal recommendation to be made about screening overweight or obese children for NAFLD, despite recent expert committee recommendations for biannual screening for liver disease in this population. However, according to Cusi, many children and teens could already have elevated liver enzymes, which may lead to NAFLD or NASH, along with the possibility for decades of liver damage.

According to a review published in *Nature Reviews Gastroenterology* and *Hepatology* by **Valerio Nobili, MD**, pediatric hepatologist, chief of the hepat-metabolic disease unit and head of the liver research unit of Bambino Gesù Children Hospital in Rome, and colleagues, the prognosis of pediatric NAFLD with advanced fibrosis or cirrhosis remains unknown. Currently, there are limited studies with long-term follow-up.

“The impressive growth of NAFLD and NASH in the pediatric population is the dramatic consequence of the increase in obesity,” Nobili told *Endocrine Today*.

“With the increasing burden of obesity, escalation of the incidence of NAFLD seems to be particularly dangerous in children. Furthermore, pediatric NAFLD is an asymptomatic and underdiagnosed condition, which, over the years, can act as a silent killer that can result in marked liver injury (including cirrhosis) and cardiometabolic syndrome,” Nobili and colleagues wrote.

Nobili’s sentiments are echoed by **Miriam Vos, MD, MSPH**, research director of the Health4Life Program at Children’s Healthcare of Atlanta, and assistant professor of medicine in the division of gastroenterology, hepatology and nutrition at Emory University School of Medicine in Atlanta.

“All gastroenterologists and pediatric hepatologists are seeing increasing referrals of children who have fatty liver disease. We recently presented some data at Digestive Disease Week in..."
May 2012 that demonstrated the prevalence of fatty liver disease is increasing more rapidly than the prevalence of obesity itself. So, the numbers are concerning and certainly do seem to be increasing,” Vos told Endocrine Today.

Vos also said there is growing evidence that sugar may play a special role in increasing both visceral adiposity and interhepatic fat; that there is necessary support for that role, and that decreasing sugar should be a primary recommendation as part of suggested lifestyle changes.

“I don’t think sugar causes fatty liver disease in someone who is not already predisposed, but sugar could be uniquely harmful in a child or adolescent who is predisposed to NAFLD or already has NAFLD. It’s a type of calorie that may be particularly harmful in that setting. There’s no downside to decreasing sugar,” she said.

Another area of concern is the long-term cardiovascular disease risk for children with fatty liver disease, Vos said. There are no natural history studies examining the long-term risk in children who develop the disease early in life.

“We can assume that somebody who gets fatty liver disease as an adolescent keeps fatty liver disease their whole life, but we don’t really know that. What we know is there are adult natural history studies that show an adult who has it will still have it 15 years later and will have increased risk of CVD events (ie, stroke or heart attack) and increased risk for cirrhosis. But, we just don’t have that kind of data in children.” Vos said.

**Varied treatment options**

Lifestyle changes are currently the cornerstone of treatment in all age groups, according to researchers.

“There’s no debate over the fact that lifestyle changes are the foundation of therapy for children with NAFLD, and it is the most effective if the parents are able to accomplish it. For example, a child who comes and gets recommendations to decrease sugar-sweetened drinks, increase vegetables and becomes more active and actually sticks to these recommendations will improve their disease substantially, and there are good studies to support that,” Vos said. “The problem lies in those children who are unable to really accomplish BMI improvement and follow lifestyle changes.”

Recent data suggest vitamin E and pioglitazone have yielded significant promise in controlled clinical trials for the treatment of NASH. According to Cusi, metformin was considered to be valuable in the management of NASH, but the drug has since failed to improve insulin sensitivity or liver histology.

“Metformin was the first pharmacologic agent that showed that liver enzymes could go down, but more recent controlled studies have shown that it has minimal effects in reversing fatty liver. Thiazolidinediones, like pioglitazone, were first shown to be effective at reducing about 50% of the amount of fat and inflammation in the liver, which was confirmed later in a larger 2-year, multicenter study,” Cusi said.
The problem with TZDs, Cusi added, is that these agents have been linked to a mild risk for heart failure. There are also controversies surrounding bone fractures, although the mechanisms are unclear. More recently, the risk for bladder cancer has led to additional questions about their use.

“It’s been shown that you would have to treat approximately 400,000 patients to cause one additional case of bladder cancer, so it’s a very low rate,” Cusi said. “The other common misconception of pioglitazone is that it increases risk for CVD. In reality, meta-analyses of the pioglitazone trials showed an 18% reduction in the overall rate of fatal and nonfatal cardiovascular events. If anything, it’s a safe approach.”

Vitamin E, insulin therapy for patients with very high-end liver enzymes, and proper diet can also reduce liver enzymes, Cusi said. Bariatric surgery is also shown to reduce liver fat and inflammation.

“I would recommend [bariatric surgery] for the treatment of NASH; I would recommend it in general, and I think it would have a positive effect,” Cusi said. “Initially, it was thought it would worsen NASH, but that’s when they were doing more aggressive surgeries — not with Roux en-Y, gastric banding or sleeve gastrectomy.”

Other suggested therapies include nutritional supplements, such as antioxidants (e.g., selenium, vitamin C, vitamin E, betaine, omega-3 polyunsaturated fatty acids). However, their efficacy has yet to be determined.

Harrison said consuming two to three cups of caffeinated coffee per day may reduce a patient’s risk for progression of fibrosis in nonalcoholic fatty liver disease. Although further research in this area is needed, in a paper published in Hepatology, Harrison and colleagues found an inverse relationship between hepatic fibrosis and the amount of caffeinated coffee consumed in a large group of nonalcoholic fatty liver disease patients. These data support findings from the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial, which showed that patients who consumed three or more cups of caffeinated coffee per day had lower rates of fibrosis progression (RR=0.47, 95% CI, 0.27-0.85).

Additionally, weight-loss drugs recently approved by the FDA, lorcaserin (Belviq, Eisai Inc.) and phentermine-topiramate (Qsymia, Vivus), have been shown to reduce weight, but their use in patients with fatty liver disease has not been tested, Cusi said.

“As long as they’re used safely and within the label, they can be helpful. The cornerstone of therapy should be lifestyle intervention plus or minus the use of pioglitazone and vitamin E until new data becomes available,” he said.

**NAFLD/NASH in clinical practice**

At Grady Hospital in Atlanta, Guillermo E. Umpierrez, MD, professor of medicine, ACTSI CIN associate program director, and section head of endocrinology and diabetes at Grady Health System at Emory University School of Medicine, said he and colleagues deal with a large number of patients with obesity and NASH on a daily basis.
"We see about 80 to 100 patients per day, and we estimate that at least 50% to 60% of them have NAFLD. The literature quotes 50% up to 80% of patients with diabetes and obesity have fatty infiltration of the liver; we agree with that," Umpierrez told Endocrine Today.

He said the rate of obesity in their diabetes clinic is "extremely high," with an average BMI of more than 33.

"We estimate that at least 50% to 60% of our patients will develop NASH. It is frequently undiagnosed because we don’t do routine diagnostic procedures to determine everybody who has NASH. That is a worldwide problem: It’s so common, we know it’s there and we just don’t pursue it as much for diagnosis in a daily clinical basis as we do for research," Umpierrez said.

He said, in his own experience, there is a lack of manpower to diagnose everyone who walks through the door. However, they consider NASH in those who have elevated liver function tests, elevated ALT and AST ratios, and are able to order some diagnostic tests. But first, they complete a hepatitis profile. If negative, Umpierrez and staff order imaging tests to diagnose fatty liver disease. This is their day-to-day practice, he added.

"We all agree that the best study would be a liver biopsy. But, this is not an easy test to be performed; our gastroenterologists don’t like to do it anymore, and patients are already sent to radiology now to avoid complications with the procedure," Umpierrez said.

He added that ultrasound is used in research but is not always accurate. Some centers at Emory University have MRS, which Umpierrez said is a better test but is not particularly cost-effective.

"We’re confronted with a tsunami. All of the problems associated with obesity such as NAFLD and diabetes are increasing and affecting a large number of populations. We are aware of all the consequences of diabetes and we are aware of the problems of NAFLD with obesity, insulin resistance and metabolic syndrome, but we do not have the tools to diagnose the large number of our patients," Umpierrez said. "It’s a very frustrating issue."

Research, guidelines needed

Vos said the challenge with moving forward is a lack of guidelines for physicians in the screening, diagnosis and treatment of NAFLD/NASH.

"We need more research on figuring out how to be effective with screening. Surely, we don’t want to screen every single overweight child in the country because that would be a large amount of money. But, we don’t want to miss anybody with fatty liver disease," Vos said.

She recommends better screening tests or additional studies to demonstrate the cost-effectiveness, targeting which patients to screen and how to go about it.

"Once a child reaches a gastroenterologist or a pediatric hepatologist, the diagnostic algorithm on how to conclude that it is fatty liver disease is fairly clear, and treatment decisions right now are not that complicated because the most important one is the lifestyle changes and following the liver disease carefully," Vos said.
Harrison also said if clinicians could give patients a clear definition of how to vigorously exercise, it could genuinely affect the disease. Additionally, there are at least five drugs in the pipeline for fatty liver that are set to target very specific mechanisms of the disease pathway.

"The future looks pretty good," Harrison said.

If the Affordable Care Act (ACA) becomes reality, the future of preventive medicine could make leaps and bounds for clinicians such as Umpierrez.

"My patient care is based at Grady Hospital, where a large number of our population is uninsured. In the diabetes clinic at Grady Hospital, 49% of our patients with type 2 diabetes have no type of coverage; they self-pay. Of the patients with type 1 diabetes we see in our adult clinic, about 75% have no insurance. The ACA will help us in a way that we will see more patients who will have some type of coverage, which will hopefully result in better care to our patients," Umpierrez said.

Cusi said the ACA is important for any preventive, long-standing chronic disease that has the potential to cause significant illness.

"Fatty liver disease in this sense might be one of those candid conditions that will benefit from the preventive medicine that this act can provide," Cusi said. "Access to preventive medicine will allow doctors to identify conditions early on; in particular, young teenagers and young adults who will have extended exposure to a fatty liver," Cusi said. – by Samantha Costa

Disclosure: Harrison is an associate editor for Hepatology, and has participated in research with Mochida, Kadmon, and Rottapharm. Umpierrez has received grant support from Sanofi-Aventis and Merck. All other researchers report no relevant financial disclosures.

For more information:

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References:

*Kenneth Cusi, MD, FACP, FACE,* can be reached at the University of Florida, 1600 SW Archer Road; rm H2; P.O. box 100226, Gainesville, FL 32610; e-mail: kenneth.cusi@medicine.ufl.edu.

*Stephen A. Harrison, MD,* can be reached at Brooke Army Medical Center, Division of Gastroenterology, 3551 Roger Brooke Drive - Fort Sam Houston, San Antonio, TX 78234; e-mail: stephen.harrison@AMEDD.army.mil.

*Valerio Nobili, MD,* can be reached at the Liver Research Institute, Bambino Gesù Children’s Hospital, Piazza S. Onofrio 4, 00165 Rome, Italy; e-mail: nobili66@yahoo.it.

*Guillermo E. Umphierrez, MD,* can be reached at General Clinical Research Center, Emory University School of Medicine, Grady Health System, 49 Jesse Hill Jr. Drive, Atlanta, GA 30303; e-mail: geumgie@emory.edu.

*Miriam Vos, MD, MSPH,* can be reached at Children’s Healthcare of Atlanta, 1405 Clifton Road NE, Atlanta, GA 30322, or Emory University School of Medicine Children’s Center Division of Pediatric Gastroenterology, Hepatology and Nutrition, 2015 Uppergate Drive, Atlanta, GA 30322; e-mail: MVOS@emory.edu.

**Should liver biopsy be used to diagnose pediatric patients with NAFLD/NASH, or should a diagnosis be made clinically through labs and imaging?**

**POINT**

The only way to discern NASH with fibrosis in children is with a liver biopsy.

Seeing an overweight child with elevated liver enzymes triggers the diagnosis of nonalcoholic fatty liver disease (NAFLD). The question is what does one do for such a child? Which child has just steatosis (NAFL) and which one has the more severe form, nonalcoholic steatohepatitis (NASH)?

In my opinion, anthropometric measures (waist circumference/waist-to-height ratio), routine lab tests (ALT/platelets), imaging (ultrasound and transient elastography) and testing panels

To make this distinction is critical in my mind for two reasons:

Long-term follow-up data suggest that individuals with fibrosis at diagnosis are at increased risk for mortality (Ekstedt M. Hepatology. 2006;44:865-873).

The only available therapeutic agent for pediatric NASH is high-dose vitamin E, which was tested only for biopsy-proven NASH (Lavine JE. JAMA 2011;305:1659-1668).

Further, the staging of NASH inflammation or fibrosis and monitoring of NASH progression or response to therapeutic interventions (diet/exercise/medication/bariatric surgery) is only possible through a tissue diagnosis. Clearly, this gold standard has its risks (bleeding/non-hepatic unintentional visceral puncture) and potential for sampling error, but despite these limitations, understanding who has NASH with fibrosis in childhood is paramount in my mind, and with today’s technology, the only way to discern the same is still through a liver biopsy.

Rohit Kohli, MBBS, MS, is an attending physician in the Liver Care Center at Cincinnati Children’s Hospital Medical Center. Kohli has received research funding from NIH from and Ethicon Endo Surgery Inc.

Imaging should be used; validate biomarkers.

It’s a very delicate question. As an endocrinologist, my first approach to the problem is using imaging before sending the child for a liver biopsy. However, imaging will not be able to diagnose NASH. Sending the patient for a biopsy is seriously considered. However, we often ask, “Is it necessary?” It’s not very well accepted by the child, has potential serious side effects and it’s very costly. About one-third of obese children who we see now have fatty liver.

Conducting a liver biopsy on all of them would not be very cost-effective. Even if NASH is diagnosed, we do not have any real treatment. How are we going to follow-up with the NASH? Are we conducting another biopsy of the child down the road? Those are the questions that are in my mind and limiting my choice.

It remains obviously very important. It’s the only way we can diagnose that there is NASH, however I think that we should make a very strong effort to use imaging and to validate biomarkers and imaging that can replace the need for biopsy in the future. I perform liver biopsy in very limited cases that are really strongly needed. In fact, over the years, I may have only performed a liver biopsy on 10 to 12 patients, but I’m not the hepatologist. Yet, the hepatologists here are not doing a lot of them, as opposed to other institutions. In the back of my mind, I always question if it is really needed, and if I do diagnose NASH, when will I have to perform a second biopsy on the child? Ultimately, this is still a very invasive technique.
Sonia Caprio, MD, is a professor of pediatric endocrinology at Yale School of Medicine, New Haven, CT. Caprio has no relevant financial disclosures.