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Best Practices for Assessing Minimally Elevated Liver Tests

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and joining me to discuss the evaluation of minimally elevated liver tests is Dr. Paul Kwo, who's a Professor of Medicine and Director of Hepatology at Stanford University.

Dr. Kwo, welcome back to the program. We always learn so much from you.

Dr. Kwo:
Thank you very much, Dr. Buch. Good to be here.

Dr. Buch:
Dr. Kwo, let's dive right in. For context, what's the range for normal transaminases?

Dr. Kwo:
The transaminases, which are liver tests or liver chemistries, are really the building blocks of our proteins that we make, and these transaminases come from the liver. The level of transaminases that you are discussing are very important because we can use this as a window into not only liver health but also overall health. And when you look at these normal levels that you'll look at on your laboratory output, you'll see an AST level and an ALT level, and the upper limit of normal, just as you were implying, very substantially, in some labs it's 25; in some labs it's actually as high as 60 or 70. And thus, this huge range makes it a challenge for physicians to really try to screen for those who may have liver disease.

When we wrote the ACG practice guidance for abnormal liver tests, the strategy we took was, what are the liver test levels where you have cutoffs, where liver-related mortality starts to increase? And we looked at populations in the US and populations outside the US, and actually, they were remarkably consistent, and so what we settled on was that for those who were female sex, the upper limit of normal is somewhere between 19 and 25 for the ALT level, and for men it's somewhere between 19 and 33. And so we used these levels because beneath these thresholds, people do not have increased risk of liver-related outcomes. This means progression to advanced liver disease, liver-related mortality, etc. And these levels that we defined are actually lower than at many commercial labs, but again, that's because now we are actually—with these levels—picking up people who may have diseases of the liver that were unrecognized, such as our most common liver disease, which is metabolic dysfunction-associated steatotic liver disease, now commonly known as fatty liver, which affects up to one third of the US depending on how it's defined. And of course, another big contributor is alcohol-associated liver disease.

Dr. Buch:
Thank you so much for that. And as a follow-up question, because I get this from community docs all the time, and they ask me, at what level should we get concerned when looking at the transaminases?

Dr. Kwo:
Yes. So when we work with our family physicians, what we tell them is the following, that if you have an ALT level that's above the upper limit of normal as we defined—so then for females above 25, for males above 33—it needs to be assessed. Okay? It doesn't mean that they have severe liver disease. One of the criticisms that has been raised is that there's a lot of people who are going to have minimal elevations of liver tests that actually aren't going to have meaningful liver disease, and to that what we say is, yes, but you at least still need to assess this level and see if there's any intervention that is required. And again, most commonly what would this be? This would be reducing metabolic risk factors, and that is lifestyle interventions, and once you get higher and higher, then obviously, the opportunities for not only other diseases of the liver but also for other liver-related outcomes becomes higher. And so we tell people,

look at your liver panel, look at your liver panel, and again, if it's above those thresholds, then at least assess it. You may choose to say everything is fine. There are plenty of people out there, say, with an ALT level of 40 to 45, who have no meaningful liver-related conditions. Nonetheless, you should continuously assess these as you see your patients periodically.

Dr. Buch:
Thank you. And the other question I get, since it's directly related, what other than liver disease can cause these minimally elevated liver tests?

Dr. Kwo:
Yes. And this is very important, because some people who come to us actually don't have a liver problem, so we generally put them in buckets. And so one of the most common buckets that we have is thyroid disease. And indeed, people who either are hyperthyroid or hypothyroid—either one—will have sometimes mildly elevated liver tests, and so when we have gone through our diagnostic algorithm for elevated liver tests, we start looking for problems outside the liver. So we check thyroid function tests. In addition, there's a common GI disorder, which actually is probably one of the most common causes of elevated liver tests in those who don't have liver disease, and that's celiac disease, and this is, again, due to a gluten hypersensitivity. And so this is actually another common disorder. And then one that we see particularly in young people is skeletal muscle disorders, and this can just be as simple as somebody who just exercises voraciously. So, there's a muscle, Dr. Buch, that I know—a muscle enzyme—that I know you're very familiar with, creatinine kinase, or CK, and that comes from muscle, but so does AST, and actually, to a small degree so does ALT. And particularly in a young person who exercises voraciously, they'll come in with these mildly elevated liver tests. And what we will do is we will then check a concomitant CK level, and if it's high, we tell these individuals, "Okay, as best you can, please do not exercise for a few days," or you know, "Please take it easy." And then we bring them back, and oftentimes, the liver tests then have, resolved themselves.

Dr. Buch:
Thank you so much for elucidating on that. So, very quickly on this one, what's the risk in missing minimally elevated liver tests?

Dr. Kwo:
Yes. So, the risks are related to why we defined our ALT cutoffs, and that is that you can actually miss significant liver disease. And in fact, let's just talk about those people who have the most common liver disease, Dr. Buch. This is metabolic dysfunction-associated steatotic liver disease massive, MASLD, or your fatty liver. So 20 percent of people with fatty liver have normal liver tests, yet still have significant fibrosis. And these are people who are at risk, again, for liver-related outcomes later in life: cirrhosis, liver cancer. They might need a liver transplant. And so it's difficult to catch everybody, but these minimal elevations may be your clue or the window into the fact that this person has a liver disorder that needs to be assessed. And again, you are assessing liver tests because you want to reduce overall liver-related mortality. But, you know, what is so prevalent now in the US are complications of the metabolic syndrome. And so metabolic syndrome affects not only the liver, but as you know, it affects the heart, kidney, just all of these different organs. There's now this, cardiometabolic syndrome that we're now learning more and more about, and the liver can be a window into this as well and can help us identify these individuals.

Dr. Buch:
Thank you for that. And on this one you partially answered it. When evaluating minimally elevated, liver tests, you talked about, metabolic dysfunction-associated static liver disease as the more common, or more likely of, illness. Which illnesses are less likely?

Dr. Kwo:
So when we have someone with minimally elevated liver tests, the first thing do is we assess them metabolically. Do you have hyperlipidemia? Is there evidence of insulin resistance? We ask people to try to address this. Again, when we find someone who has minimally elevated liver tests and we want to see if they can get better, we don't need to do a complete evaluation right away, but we'll say, "Okay, stop your alcohol. Concentrate more on a better metabolic lifestyle. Stop your supplements," which is another big contributing factor to elevated liver tests. You know, people—and I'm sure you see this, Dr. Buch—people love their supplements. They buy them because they see in the nutrition store this is natural, and as I like to tell people, a great white shark is also natural, but it's not necessarily safe. And so we try to tell everyone, "Come off of all of your supplements for a period of time," and then we observe them over time. For minimal elevations, then actually they may just resolve themselves, and if they do, great. That's it. And then, for instance, if they really want to resume their supplements—they may feel better on them—once we see liver tests that are normal, what we do is we start introducing something back, but only one at a time—one intervention at a time—so that we can monitor to make sure we can really drill down on what is driving that minimally elevated liver test. And again, with this then, generally, that provides an answer for the vast majority of people that we see with elevated liver chemistries.

Dr. Buch:
Thank you for that. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr.

Paul Kwo about evaluating minimally elevated liver tests.

So, Dr. Kwo, what workup do you recommend for minimally elevated liver tests?

Dr. Kwo:
So for minimally elevated liver tests, we look at the metabolic alcohol risk factors. We'll look for two common viral diseases, hepatitis B and hepatitis C. So, again, we do, unfortunately, have a substantial substance use problem in the United States, and viral hepatitis still is a substantial public health threat for us, so we look for serologies for hepatitis B and hepatitis C. In addition to stopping our supplements, we also look for an iron overload. So there is a genetic disorder, hemochromatosis. One out of 10 Caucasians carry one gene for this disorder. Fortunately, the penetrance or the disease expressing itself is not very high, but we like to look to see and make sure that the iron panel is also within normal limits in these people with minimally elevated liver tests.

Dr. Buch, once the liver tests become more substantially elevated—say the ALT and AST are two times, three times the upper limit of normal—we're looking a little bit more broadly. But again, we want to just make sure we have in these minimal or borderline elevated ALT and AST, that we've assessed the most common causes of AST and ALT. And again, a period of observation is perfectly reasonable under these circumstances, provided you're confident that they don't have advanced liver disease.

Dr. Buch:
So then after that occurs—the basic workup—the next workup would be for things like celiac disease, thyroid disease, etc.

Dr. Kwo:
That's right. And if their liver tests stay high, then we'll add autoimmune markers and some of the rare inherited disorders, alpha-1 antitrypsin and Wilson's disease. But these are rare genetic disorders, and they constitute less than one percent of all elevated liver tests, so we generally—for minimal elevations—don't do them right away, though there is data to suggest that if you ordered everything at once, it's roughly the same cost, but just recognizing that it's probably not going to be fruitful at the very beginning. And again, this is particularly for those who have minimal elevations.

Dr. Buch:
We're in the last few minutes of our conversation, Dr. Kwo. Do you have any additional thoughts you'd like to share?

Dr. Kwo:
Yes. Just that the liver is a window to your health, and you can look at your liver panel, and you can look at your patient's liver panel, and it really gives you an opportunity to identify diseases not only within the liver but outside the liver as well. And again, if you have a minimally elevated AST or ALT, it doesn't mean you have a serious condition, but you should think of this as health maintenance. It's an opportunity to make things better. And if you improve your liver health, you're going to improve your overall health as well.

Dr. Buch:
Thank you so much. I want to thank my guest, Dr. Paul Kwo, for an excellent discussion on how we can properly evaluate minimally elevated liver test. Dr. Kwo, it's always a pleasure speaking with you.

Dr. Kwo:
It's good to be with you again, Dr. Buch.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening, and looking forward to learning with you again very soon.