Lean and Nonobese NAFLD/NASH From a Hepatologist's Point of View

To the Editor:

For NAFLD/NASH pathogenesis, it is a prerequisite, first, to develop fatty liver, which is then unusually vulnerable to various second hits or injury. Insulin resistance is a universal finding for both simple steatosis and NASH.

This group of lean patients should be regarded as having a secondary causal fatty liver (such as Wilson disease and Celiac disease) and excluded from nonalcoholic fatty liver disease (NAFLD) patients due to both the shortcomings in the design of the study and inadequate questioning of the underlying toxic causes (such as hidden alcohol consumption, use of herbal supplements, protein shakes consumed in fitness centers, and beverages with high protein content sold in ordinary supermarkets).

I read with great interest the article published by Shi et al.[1] In this meta-analysis, a total of 45 studies were included. Of the 55,936 lean/nonobese subjects, 7351 NAFLD patients were diagnosed. Overall, the pooled NAFLD prevalence of the lean or nonobese population was 10.2% and 15.7%, respectively, in this study. Shi and colleagues reported that lean/nonobese NAFLD patients had significantly lower rates of hypertension, lower uric acid and fasting plasma glucose, and a higher level of high-density lipoprotein than nonlean/obese patients. Similarly, Shao et al[2] showed that nonobese NAFLD is paradoxically associated with improved metabolic and pathologic features at diagnosis, but worse prognosis relative to obese NAFLD.

In contrast, NAFLD is likely in type 2 diabetes mellitus, and it is one of the consequences of obesity.[3–5] Currently, the prevalence of NAFLD in the obese population is nearly 95%. NAFLD is also very prevalent in overweight nonobese individuals [body mass index (BMI) $\geq 25\ kg/m^2$]. In daily practice, factors contributing to NAFLD include sedentary lifestyle, and increased consumption of foods with high-fat and high fructose corn syrup content.[4–7] The primary limitation of the above lean and nonobese NAFLD studies is the inclusion of people who are overweight (BMI: 25 to 30) and normal weight (BMI: 18.5 to 25). It is no wonder that the people who are overweight also have insulin resistance, and therefore they are of NAFLD. In my opinion, it is not wise to use BMI values as the key determinant to group patients in such studies. This approach leads to erroneous grouping of athletic people whose BMIs are too high, but have low fat mass and high muscle mass, which, in turn, could be mistaken as obese. For this reason, there is no real patient homogenization in such studies. The mechanisms underlying NAFLD/nonalcoholic steatohepatitis (NASH) pathogenesis, which include an inappropriate fat storage or ectopic fat accumulation, and the primary abnormality being most likely insulin resistance, lead to the accumulation of triglycerides within the hepatocytes.[3,7,8] After the first hit of steatosis, the second hit of both insulin resistance and oxidative stress leads to hepatocyte injury and inflammation. For NASH pathogenesis, it is a prerequisite, first, to develop fatty liver, which is then unusually vulnerable to various second hits or injury. Insulin resistance is a universal finding for both simple steatosis and NASH. An important limitation of such studies is the frequency of insulin resistance seen in these studies, which is ambiguous and controversial. However, due to the reasons I have cited above, NAFLD/NASH cannot exist without insulin resistance. Insulin resistance and peripheral lipolysis cause an increased free fatty acid (FFA) pool in the circulation. This pool is one of the major sources of hepatic triglycerides. FFAs are also the major source of hepatic mitochondrial, peroxisomal, and microsomal reactive oxygen species production. It has been reported that increased hepatic and serum FFA concentrations promote hepatic and systemic insulin resistance by the activation of PKC-theta, and by the serine phosphorylation of insulin receptor substrates.

In another study, Wang et al[9] reported that, more importantly, nonobese patients had a significant higher prevalence of advanced fibrosis ($F \geq 3$) and a trend of higher degree of ballooning. In the absence of the metabolic risk factors, hepatopathology with severe injury brings methionine-choline–deficient (MCD) diet-fed or murine steatohepatitis model to my mind.[10] Historically, there are several types of animal models used for NAFLD studies, and these are mainly characterized as follows: genetically disturbed or murine fatty liver, MCD diet-fed mice or murine steatohepatitis model, and feeding high-fat and/or sucrose diets with or without high caloric intake model. Although some of the histologic changes that develop in these models exhibit features of human NAFLD, the underlying pathogenesis of fat accumulation and consequent cellular injury may not reflect the mechanisms of human disease. For example, the frequently used MCD diet model induces many histologic abnormalities described as similar to human NASH, but the model is not associated with insulin resistance, and rodents treated with this diet typically lose, rather than gain, weight. However, insulin resistance is a universal feature of patients with NASH, and the MCD model is not insulin-resistant and not obese. MCD mice have increased insulin hypersensitivity, and their serum has both insulin and glucose levels lower than mice fed a standard diet. In contrast, NAFL/NASH seen in people results from reduced physical activity (sedentary lifestyle) and excessive calorie intake. In the next phases, the severity of the diseases varies depending on the source of the excessive calorie intake.

In conclusion, this group of patients (lean with fatty liver) should be regarded as having a secondary causal fatty liver (such as Wilson disease and Celiac disease) and excluded from NAFLD patients due to both the shortcomings in the design of the study and inadequate questioning of the underlying toxic causes (such as hidden alcohol consumption, use of herbal supplements, protein shakes consumed in fitness centers, and beverages with high protein content sold in ordinary supermarkets).

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The author declares that there is nothing to disclose.
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REFERENCES

1. Shi Y, Wang Q, Sun Y, et al. The prevalence of lean/nonobese nonalcoholic fatty liver disease: a systematic review and

meta-analysis. *J Clin Gastroenterol*. 2020; 54:378–387.
2. Shao C, Ye J, Li F, et al. Different predictors of steatosis and fibrosis severity among lean, overweight and obese patients with non-alcoholic fatty liver disease. *Dig Liver Dis*. 2019;51:1392–1399.
3. Basaranoglu M, Neuschwander-Tetri BA. Nonalcoholic fatty liver disease: clinical features and pathogenesis. *Gastroenterol Hepatol (N Y)*. 2006;2:282–291.
4. Basaranoglu M, Basaranoglu G, Sabuncu T, et al. Fructose as a key player in the development of fatty liver disease. *World J Gastroenterol*. 2013;19:1166–1172.
5. Basaranoglu M, Basaranoglu G, Bugianesi E. Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction. *Hepatobiliary Surg Nutr*. 2015;4:109–116.
6. Tetri LH, Basaranoglu M, Brunt EM, et al. Severe NAFLD with hepatic necroinflammatory changes in mice fed trans fats and a high-fructose corn syrup equivalent. *Am J Physiol Gastrointest Liver Physiol*. 2008;295:G987–G995.
7. Basaranoglu M, Basaranoglu G, Sentürk H. From fatty liver to fibrosis: a tale of "second hit". *World J Gastroenterol*. 2013;19:1158–1165.
8. Başaranoğlu M, Örmeci N. Nonalcoholic fatty liver disease: diagnosis, pathogenesis, and management. *Turk J Gastroenterol*. 2014;25:127–132.
9. Wang AY, Dhaliwal J, Mouzaki M. Lean non-alcoholic fatty liver disease. *Clin Nutr*. 2019;38:975–981.
10. Basaranoglu M, Kayacetin S, Yilmaz N, et al. Understanding mechanisms of the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2010;16: 2223–2226.

EUS-directed Transgastric Endoscopic Retrograde Cholangiopancreatography (EDGE)

The First Learning Curve

To the Editor:

We read with extreme interest the paper of Dr Tyberg et al[1] related to biliary endoscopy in patients with Roux-en-Y anatomy after gastric bypass for obesity (EDGE). The elegant message inspired us a speculation: does the general concept of learning curve apply to every medical or surgical procedure? We think that the answer is quite complicated.

Generally speaking, we consider a procedure to be routine when a significant number of cases are treated by an operator or by a group of operators in a single center; usually, the procedure is performed almost daily and it is, within certain limits, suitable for standardization.[2] This is the setting where the concept of learning curve applies.[3] For example, we know that an operator must perform a minimum number of procedures to acquire and maintain proficiency in colonoscopy or endoscopic retrograde cholangiopancreatography (ERCP); also the caseload of the center plays a role in improving results and reducing complications, even if numbers are not the only thing that matters.[4] This concept suits almost every "surgical" procedure and every manual skill; anyway, some peculiar procedures do not fit the routine definition, mainly because of their rarity.

The EDGE procedure belongs to the latter group: in a high-volume center, like the authors' one, only 19 cases were described in 3 years.[1] Fortunately, even these rare procedures can be split in a series of discrete technical steps, each one requiring skill that can be developed in other interventions. This concept compares to the modular learning in playing a musical instrument.[5]

Furthermore, the authors speculate in the discussion that the procedure became smoother after the technical improvement of the lumen apposing stent with the implementation of the "hot" system. So, the evolution of the device played an essential role in accelerating the procedure, as well as the increased confidence of the operator with the stent during time.[1] To be honest, we believe that in the time between the first and the last procedure of the series, the operator (Dr Kahaleh) implanted several lumen apposing stents for other indications and performed many difficult ERCPs. We guess we are not far from real, knowing the colleague in person and his high level of skill.

We appreciate the authors' effort to try and analyze this setting objectively, but it is our opinion that all the other allied procedures that the operator performed in the meantime should be included in the learning curve. We believe it is fair to say that this kind of procedures, as well as their specific learning curve, are poorly suitable for standardization. We are far from thinking that performing more procedures does not increase the confidence of the operator, and there will always be some particular tricks in every distinct intervention, but the way to deal with these peculiar situations passes through proficiency in interventional endoscopy, with continuous and structured training. It is unlikely to receive a specific coaching for each contingency: only an expert in ERCP, interventional EUS and much more, can approach complex clinical scenarios, facing each step with the owned and mastered skills and being able to deal with all possible complications. Proficiency, at the very essence, is a complex and emergent property and, speaking of learning and training, "wax on, wax off" is still the way to go.[6]

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REFERENCES

1. Tyberg A, Kedia P, Tawadros A, et al. EUS-directed transgastric endoscopic retrograde cholangiopancreatography (EDGE): the first learning curve. *J Clin Gastroenterol*. 2020;54:569–572.
2. Routine. Oxford dictionary, 2020. Available at: Oxfordlearnersdictionaries.com. Accessed August 20, 2020.
3. Hopper AN, Jamison AM, Lewis WG. Learning curves in surgical practice. *Postgrad Med J*. 2007;83:777–779.
4. Forbes N, Mohamed R, Raman M. Learning curve for endoscopy training: is it all about numbers. *Best Pract Res Clin Gastroenterol*. 2016;30:349–356.
5. Acoustical Society of America. How Do Musician's Brains Work While They Play? 2020. Available at: https://neuroscienc enews.com/musicians-playing-neuroscience-5672/. Accessed August 20, 2020.
6. Avildsen JG. *The Karate Kid*. Culver City, CA: Columbia Pictures; 1984.