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NAFLD-Related Hepatocellular Carcinoma and the Four Horsemen of the Apocalypse

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Nonalcoholic fatty liver disease (NAFLD) has become the most important cause of chronic liver disease in the United States, affecting 25% of adults in the country. The rest of the world does not lag behind. The Americas, Asia, and the Middle East show higher rates of NAFLD than the United States, and Europe and Africa suffer a rapid escalation of "fatty livers."[1] Just as it is evident that control of NAFLD currently represents one of the biggest challenges in liver disease, it is also evident that NAFLD represents a large spectrum of diseases and that the progression to cirrhosis and hepatocellular carcinoma (HCC) occurs in a minority of affected individuals. Identifying those individuals to better monitor and screen them as well as understand the underlying mechanisms of disease progression in that setting is a highly relevant issue and one the scientific community is eager to define. It is in this context that Kanwal et al.[2] in this issue of Hepatology, evaluated the role of metabolic traits in the progression of NAFLD to cirrhosis and HCC. Their findings expose a "hepatocalyptic" resemblance to a modern-day four horsemen, with diabetes, obesity, dyslipidemia, and hypertension all contributing together and independently to the destruction of the liver.

Obesity alone is associated with increased overall mortality from all cancers, and HCC is no exception. However, the presence of obesity and dyslipidemia in the setting of NAFLD has a unique impact in the liver. Both maladies increase lipid accumulation, with subsequent generation of reactive oxygen species and endothelial reticulum stress, all of which leads to inflammation and fibrosis.[3] Moreover, obesity leads to dysregulation of leptin, a hormone released in relation to satiety that contributes to the production of a catabolic state.[4] Alterations in leptin regulation can lead to insulin resistance, with an aggressive form of hepatic steatosis as well as an increase in adipocyte production of tumor necrosis factor-α (TNF-α), a proinflammatory cytokine related to liver fibrosis and HCC. TNF-α can induce activation of c-Jun N-terminal kinase, leading to impairment of the normal insulin receptor signaling, as well as interact with nuclear factor kappa B to promote the transcription of genes involved in apoptosis, inflammation, proliferation, and angiogenesis.[4] An obesity-related increase in the insulin-like growth factor has also been associated directly with the promotion of HCC through modulation of cell growth and migration.[3,5]

Hypertension as such is unlikely to lead to fibrosis progression or HCC development and likely represents an expression of the conundrum of the metabolic syndrome. However, the association of hypertension with

Abbreviations: HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.

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NAFLD is of dramatic significance; after all, the most common cause of death in individuals with NAFLD is cardiovascular disease.[6]

Diabetes represents a unique horseman because it can significantly increase progression to HCC alone as well as dramatically augment the effects of the other metabolic traits. In the study by Kanwal et al.[2] diabetes had the strongest association with HCC, a finding reported by multiple groups, including the authors.[7,8] It is thought that all the insulin-related pathogenic events mentioned above, including insulin-like growth factor signaling pathway modulation, contribute to the effect of diabetes on HCC progression in the setting of NAFLD. Diabetes also promotes hepatocarcinogenesis through activation of inflammatory cascades with production of proinflammatory cytokines, which cause genomic instability and inhibit apoptosis of hepatocytes.[9] In addition, associations with bacterial translocation and increased iron deposition in the setting of diabetes and NAFLD can also exacerbate the progression to cirrhosis and HCC.[3] Indeed, although most studies suggest that modifying the endocrine impact of diabetes with metformin or statins improves liver health in this setting, the underlying mechanisms are far from clear.[3,10]

A unique aspect of Kanwal et al.'s study is the association of obesity,[2] dyslipidemia, and particularly diabetes with noncirrhotic HCC development. Most theories of HCC development, diabetes, and obesity relate to inflammatory models; therefore, this finding brings to light the need for further research aimed to understand the molecular aspects related to noncirrhotic HCC in the setting of NAFLD. Interestingly, a recent European study found an inverse association between noncirrhotic HCC and the presence of diabetes, which leads to speculation that epigenetic and environmental variables play a major role in the interrelation between diabetes, NAFLD, and HCC.[11]

In the quest to identify a specific cohort of individuals to follow closely for the early identification of liver-related complications, the authors propose to focus on individuals with multiple metabolic traits. This represents a reasonable initial approach, but an approach faced with the dilemma of having a population that is still too large to focus on. Approximately 40%-70% of individuals with diabetes have evidence of NAFLD.[1] In the study by Kanwal et al.[2] that number was closer to 40%. Because of the nature and interrelation of diabetes with obesity, hypertension, and dyslipidemia, a large number of these individuals will present multiple traits. In the study, approximately 20% of participants had all four traits. However, individuals were initially identified for inclusion based on elevated liver enzymes, likely leaving a much higher number of participants with steatosis findings associated with diabetes with unclear prognosis. Moreover, those with lean NAFLD or of different ethnic origin will likely have risk factors not taken into account in this study.

More importantly, the study highlights the need for a better understanding of the effect of metabolic traits in HCC development and the need for multinational and multiethnic cohorts. The study by Kanwal et al.[2] was performed in a mainly white male population of veterans with NAFLD identified by elevated liver enzymes. Indeed, 95% of study participants were men, and 69% of these men were white. The mean body mass index in the population was 31.

Overall, the findings get clinicians a step closer to a better stratification of individuals with NAFLD who are at risk for complications. Sadly, the complex cascade of events leading to NAFLD-related complications and the vast range of diseases that are grouped into what we call "NAFLD" will require further and deeper research to identify the most destructive horsemen.

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