

Editorial

Interactions among Hepatic Steatosis, Inflammation, and Insulin Resistance: Beyond Common Sense

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Editorial

Non-alcoholic fatty liver disease (NAFLD) is a growing health problem, and may progress to liver cirrhosis and hepatocellular carcinoma after the formation of steatohepatitis. Much evidence suggests that NAFLD is highly prevalent in obese populations. For instance, the prevalence of NAFLD increases from 10 to 24 percent of the general population to 57.5 to 74 percent of the obese population [1,2]. Because of this, the interaction between fat deposition and insulin resistance, two critical aspects commonly associated with obesity, appears to underlie the development of NAFLD and the progression of steatohepatitis. Beyond common sense, recent evidence also supports the involvement of new mechanisms in the pathogenesis of NAFLD, as well as steatohepatitis.

As it is generally accepted, insulin resistance or insulin, at the elevated levels, acts through stimulating activities of transcription factors such as sterol regulatory element-binding protein 1c (SREBP1c) and carbohydrate responsive element-binding protein (ChREBP) to increase liver expression of genes for lipogenic enzymes including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). Additionally, insulin resistance, at both hepatic and systemic levels, may also decrease fatty acid oxidation through the mechanisms involving inhibition of carnitine palmitoyltransferase 1 (CPT1) activity. These events, along with or without a relative decrease in the release of hepatic triglycerides and/or a relative increase in the uptake of free fatty acids, lead to fat deposition as the result of the net outcome of liver fat metabolic pathways. Once hepatic steatosis forms, fat deposition may serve as a primary "hit" to initiate or exacerbate deleterious metabolic consequences at both hepatic and systemic levels. In support of this, fat deposition in hepatocytes is shown to trigger inflammatory responses in cultured hepatocytes [3,4] and to induce liver insulin resistance in mice [5]. In terms of liver inflammation that drives the progression of simple steatosis to steatohepatitis, it has been shown that fat deposition in hepatocytes stimulates reactive oxygen species (ROS) production, thereby triggering oxidative stress and activating hepatocyte signaling through the nuclear factor KB (NF-KB) and/or Jun N-terminal kinase 1 (JNK1) pathways.

Based on common sense described above and reviewed elsewhere, there likely exists a vicious cycle among hepatocyte fat deposition, liver inflammatory response, and hepatic insulin resistance in the development of steatohepatitis. While clear-cut causal relationships among aspects of NAFLD within the vicious cycle remain to be investigated, recent evidence also indicates that fat deposition is not necessarily accompanied by insulin resistance [6,7]. Results from certain genetically modified mice even suggest an inverse correlation between hepatic fat deposition and insulin resistance [8,9]. Therefore, additional mechanisms must exist beyond common sense regarding interactions among hepatic steatosis, inflammation, and insulin resistance. This editorial emphasizes the two following views.

Firstly, the composition of fat deposited but not fat content appears to control the status of hepatic inflammatory response. This view is supported by the results from both human subjects and animal models in which liver inflammation is regulated in a hepatic steatosis-independent manner [10,11]. Consistently, treatment of Huh7 hepatocytes with palmitoleate, a monounsaturated fatty acid, increases steatosis but decreases the phosphorylation of inflammatory signaling through the JNK1/2 [12]. When compared with previous studies in which a causal relationship between fat deposition and the inflammatory response is established in various hepatocytes [3,4], the study on treating Huh7 cells with palmitoleate suggests that the differences in the types of fatty acids, i.e., palmitate vs. palmitoleate for triglyceride synthesis, determine the outcome of hepatocyte inflammatory response [12]. As substantial evidence, over-expressing human acyl-CoA: diacylglycerol acyltransferase specifically in the liver increases hepatic steatosis without altering liver inflammatory response in mice [9]. Similar findings have also been obtained in mice, in which enhancing liver mitochondrial fatty acid oxidation reveres obesity-associated glucose intolerance and liver inflammatory response but does not alter hepatic steatosis [13].

Secondly, hepatocyte insulin sensitivity inversely correlates with the status of the inflammatory response better than with hepatocyte fat deposition. For nearly two decades, inflammation has been implicated as a causal factor of insulin resistance. One likely mechanism is that in a given target tissue the infiltrated/resident macrophages and/or other inflammatory cells are usually in a proinflammatory state and express high levels of proinflammatory cytokines. The latter disturb insulin signaling through direct activation of the JNK1 and IkB kinase 2 (IKK2)/NF-κB pathways, leading to serine phosphorylation of insulin receptor substrate (IRS) 1 [14,15]. Given the dissociation of fat deposition and the status of the inflammatory response as discussed above, it is easier to accept the dissociation of fat deposition and insulin resistance. In many recent studies, insulin resistance is indeed inversely correlated with fat deposition. To be noted, with almost no exception, insulin resistance is positively correlated with increased inflammatory response in both in vitro and in vivo [9,13,16].

 $\label{eq:any} A number of approaches including weight loss, diet supplementation,$

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metformin, insulin sensitization by thiazolidinediones, bariatric surgery, and liver transplantation have been considered for managing NAFLD. At this point, the effective treatment for steatohepatitis is still lacking. Given the views discussed above, it may only be a good wish to use one treatment or combined treatments to reverse all aspects of NAFLD and/or to prevent the progression of steatohepatitis. Nonetheless, due to the importance of the inflammatory status but not any other aspects of NAFLD in critically driving the development of steatohepatitis, anti-inflammatory approach could be considered as the top priority in managing NAFLD. From nutrition perspective, a wide variety of anti-inflammatory food components and natural products, i.e., fish oils and berberine, may therefore be good choices.

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