LETTER

Non alcoholic fatty liver disease two-hit process: multifactorial character of the second hit

Dear Editor

We appreciate the interest of Polyzos and collaborators[1] in our review. It is true that only one of the recognized mechanisms cannot explain the pathogenesis of non alcoholic fatty liver disease (NAFLD) in all affected patients. As mentioned in the review, NAFLD represents a continuum of hepatic injuries, which progress from simple fatty liver to steatohepatitis (NASH). According to the most widespread and prevailing model of "two-hit hypothesis", the "first hit" involves lipid accumulation in the hepatocytes[2-4]. Insulin resistance is suggested to be the key pathogenic factor for the development of hepatic steatosis. The "first hit" increases the vulnerability of the liver to many factors that constitute the "second hit" and promote hepatic injury, inflammation and fibrosis. Oxidative stress and subsequent lipid peroxidation, proinflamatory cytokines, adipokines and mitochondrial dysfunction are included among these factors. Consequently, your argument for the second hit is technical, since the "second hit" is a constitution of many hits as mentioned above. We highlight the role of oxidative stress since it has been proposed as a main instigator triggering the progression of steatosis to steatohepatitis. Many studies demonstrate that oxidative stress is a prominent feature of NASH [5-8]. In addition, it has been proposed that genetic and environmental factors trigger progression to NASH through the enhanced production of reactive oxygen or/and nitrogen species (ROS/RNS)[7]. Furthermore, bacterial overgrowth, changes in gene expression and rennin-angiotensin system (RAS) are suggested as potential contributors to hepatic steatosis and inflammation. Adipose tissue, especially visceral adiposity, appears to play an important pathogenetic role. It is now recognized as an endocrine, autocrine and paracrine organ that secretes adipokines. Our review provides epidemiological and experimental data on the role of adiponectin, leptin, resistin and cytokines like TNF-a, IL-6, in NAFLD. However, a detailed discussion of each of these factors is beyond the scope of this paper. Finally, it is important to note that all the mentioned mechanisms are not mutually exclusive, but instead of likely act in a coordinated and cooperative manner to hasten the development and progression of NAFLD.

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References

1. Polyzos SA, Kountouras J, Zavos Ch. The multi-hit process and the antagonistic roles of tumor necrosis factor-alpha and adiponectin in nonalcoholic fatty liver disease. Hippokratia 2009; 13: 127 (letter)
2. Qureshi K, Abrams GA. Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of nonalcoholic fatty liver disease. World J Gastroenterol 2007; 13: 3540-53
3. Duvnjak M, Lerotic I, Barsic N, Tomasic V, Virovic Jukic L, Velagic V. Pathogenesis and management issues for non-alcoholic fatty liver disease. World J Gastroenterol 2007; 13: 4539-50
4. Schreuder TC, Verwer BJ, van Nieuwkerk CM, Mulder CJ. Non-alcoholic fatty liver disease: An overview of current insights in pathogenesis, diagnosis and treatment. World J Gastroenterol 2008; 14: 2474-86
5. Albano E, Mottaran E, Vidali M et al. Immune response towards lipid peroxidation products as a predictor of progression of non-alcoholic fatty liver disease to advanced fibrosis. Gut 2005; 54: 987-93
6. Seki S, Kitada T, Yamada T, Sakaguchi H, Nakatani K, Wakasa K. In situ detection of lipid peroxidation and oxidative DNA damage in non-alcoholic fatty liver diseases. J Hepatol 2002; 37: 56-62
7. Begriche K, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. Mitochondrion 2006; 6: 1-28.
8. Albano E, Mottaran E, Occhino G, Reale E, Vidali M. Review article: role of oxidative stress in the progression of non-alcoholic steatosis. Aliment Pharmacol Ther 2005;22 Suppl 2: 71-3