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Non-Alcoholic Fatty Liver Disease, Cryptogenic Cirrhosis and Type-2 Diabetes Mellitus: How are They Related?!

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Opinion

A growing number of published papers consider the non-alcoholic fatty liver disease (NAFLD) and cryptogenic cirrhosis as the immediate offspring of Type 2 diabetes mellitus (T2DM). NAFLD is the most common liver disorder in developed countries, where up to 80% of obese people have the disease. Cirrhosis is defined as the advanced stages of hepatic fibrosis with characteristic distortion of hepatic architecture in addition to numerous regenerative nodules. Cirrhosis without an apparent cause (eg, alcoholic liver disease, viral hepatitis B & C, autoimmune hepatitis, Wilson' s disease and so on ….) has been labeled as cryptogenic [1,2]. After presentation and identification of metabolic syndrome as a distinct clinical entity and its final outcome, that is T2DM, the surging prevalence of NAFLD and cryptogenic cirrhosis was considered as a direct complication of T2DM [3-9]. In a study conducted by Younossi, of 132 patients with NAFLD, 44 subjects (33%) were reported to have established T2DM [10]. Of those forty- four diabetic patients with NAFLD, 11 were reported to be affected by frank cryptogenic cirrhosis. Going through the paper, the reader would immediately suppose that, one out of three type 2 diabetic patients have had concomitant end-stage cirrhosis of the liver. In a review article, Cusi K. proceeded further up and stated that approximately 70% of T2DM patients had fatty liver, and the non-alcoholic steatohepatitis was suggested as the leading cause of end- stage liver disease in persons with T2DM.The author eventually concluded as if the NASH is the straightforward "complication" of T2DM!! [11].

In Verona diabetes study from Paris, de Marco made an utterly confusing statement that, end-stage hepatocellular failure due to cryptogenic cirrhosis was the fourth leading cause of death in type 2 diabetes subjects. In another case-control study carried out by Poonawala etal., from forty-nine patients defined as cryptogenic cirrhosis, 47 percent reported to have concomitant T2DM.They easily concluded that one out of two cases of cirrhosis with undetermined etiology (cryptogenic) was affected by T2DM, and this constellation was presented in such a way that one would conceptualize that T2DM was the cause and NAFLD and cryptogenic cirrhosis were the direct consequence [12]. It seems as though these authors completely ignored the already-settled issue of glucose intolerance and mild diabetes in most cases of end-stage liver disease. Contrary to the mentioned studies, in a more reasonable cohort study carried out in Japanies workers, NAFLD was presented as a strong predictive risk for T2DM, which means that T2DM would develop many years after commencement of NAFLD [13].

In a prospective observational study published recently by our team, a total of 132 overt T2DM patients attending a university hospital diabetes clinic were thoroughly investigated for the presence of concomitant NAFLD and cryptogenic cirrhosis. We had the unique opportunity to carry out the study in a community in which, alcohol production, distribution, vending and consumption were strictly banned religiously, ritually and legally. Taking full advantage of this opportunity, we were able to confidently eliminate the likelihood of alcoholic liver disease as a possibly neglected confounding variable in relevant studies conducted in western societies. To our surprise, the study revealed that, only six percent of T2DM subjects were affected by mild NASH and less than 1.5% had concomitant cirrhosis or better to say overt liver failure, of which one patient tested positive for HCV Ab and the other disclosed later to have been consuming alcohol for many years in the past once living abroad [14]. Contrary to previously mentioned studies, there are some masterly designed and devotedly conducted studies where a close agreement could be found with our study. With the aim of examining the already reported increased risk of NAFLD and hepatocellular carcinoma in T2DM, El-serag, et al. [15] carried

out a meaningful case-control study demonstrating that, diabetes mellitus does increase the risk of hepatocellular carcinoma, but only in the presence of other risk factors such as hepatitis B or C or alcoholic cirrhosis [15]. This was exactly what we were trying to highlight. We believe that T2DM has, per se, nothing to do with NASH, cryptogenic cirrhosis or hepatocellular carcinoma. As a matter of fact, T2DM, liver steatosis, NASH and cryptogenic cirrhosis are all the victims of a prime pathogenic culprit; the devastating modern- time human health catastrophe, the insulin resistance syndrome. A must-to-know issue is the true location of T2DM in the Jigsaw of metabolic syndrome; a matter that might have been the major source of all partialities and errors in relevant studies. As a component of highly active metabolic syndrome, NAFLD and NASH need considerable, persistent and protracted hyperinsulinemia for vivid development and significant progression towards the cryptogenic cirrhosis.

Right in contrast to galloping NASH, a state of relative insulin deficiency is needed to induce impairment of fasting plasma glucose (IFG) and then overt T2DM. In other words, for development of T2DM, the process of metabolic syndrome and hyperinsulinemia must be loosened up or becomes somehow aborted. Therefore, from pathophysiologic point of view, T2DM and progressive NASH are situated on the opposite ends of the spectrum in metabolic syndrome. According to the results of our study and the previously discussed pathophysiologic principles, we would reasonably suggest that, if the alcoholic liver disease, as the major and easily overlooked confounding variable, becomes practically eliminated from the studies,T2DM, per se, would seldom cause a deep-seated cirrhosis or fully-developed end-stage liver failure. We, in fact, consider the rapidly growing incidence and the surging prevalence of cryptogenic cirrhosis as the cumulative impacts of alcoholic liver disease and the damaging effects of unleashed hyperinsulinemia of insulin resistance syndrome, and in- between the T2DM is an innocent by-stander despite of being frequently seen along with cryptogenic cirrhosis. It seems as though these authors completely ignored the already-settled issue of glucose intolerance and mild diabetes in most cases of end-stage liver disease. We believe that, T2DM has, per se, nothing to do with NAFLD, cryptogenic cirrhosis or hepatocellular carcinoma. The supposition of any pathogenic link between T2DM and NAFLD is basically erroneous. Along the evolutional path of metabolic syndrome, from birth to death, NAFLD stands on the first half of this path, whereas T2DM gradually appears over the second. NAFLD develops and progresses on account of conspicuous hyperinsulinemia, while the impaired fasting glucose and overt T2DM occur once the pancreatic B- cells become exhausted and the excessive insulin secretion begins to fade away. Therefore, NAFLD and T2DM are, indeed, the two opposite aspects of a single pathophysiologic coin, that is, the insulin resistance syndrome. We would suggest that, in recent studies addressing the interrelationship between T2DM and NAFLD, two major background variables are being neglected; the pervasive and obviously difficult to document under- reported alcohol consumption and the newly emerged, worldwide insulin resistance syndrome. In effect, the horrendous prevalence of NAFLD and cryptogenic cirrhosis is the summation effects of surreptitious alcoholic liver disease and the hyperinsulinemic phase of metabolic syndrome, whereas, the T2DM is an innocent by-stander playing probably no significant role in the pathogenesis of non-alcoholic liver disease and cryptogenic cirrhosis.

Keywords: Type-2 diabetes mellitus, Alcoholic liver disease, Cryptogenic cirrhosis, Metabolic syndrome

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