Antioxidant defence mechanisms: new players in the pathogenesis of non-alcoholic steatohepatitis?

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ABSTRACT

This comment discusses the study by Videla and colleagues in this issue of Clinical Science in which they have analysed surgical liver biopsies from obese patients with non-alcoholic fatty liver disease and demonstrate that fatty liver is associated with a state of oxidative stress and a decreased antioxidant activity. As the disease progresses to steatohepatitis, the defect in antioxidant systems increases. Thus efficiency of antioxidant defence mechanisms, by setting the threshold at which pro-oxidants would become injurious, might represent a determining factor for disease progression from stable steatosis to steatohepatitis.

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological condition often seen in patients with obesity and insulin resistance [1,2]. The pathological spectrum of NAFLD comprises hepatic steatosis alone (fatty liver), hepatic steatosis with lobular inflammation and non-alcoholic steatohepatitis (NASH), the latter being characterized by steatosis, necrosis and degeneration of hepatocytes, inflammation and pericellular and intralobular fibrosis [1]. Although there is a continuum in disease progression, only a fraction of patients with fatty liver will develop NASH. Major advances have been made in understanding the physiopathological characteristics of NAFLD; however, the pathogenesis of this syndrome remaining elusive. In particular, little is known about the factors responsible for the transition from benign steatosis to progressively fibrosing steatohepatitis. As a consequence, the clinician has no tool to identify patients at risk of such progression.

Oxidative stress has been proposed as a likely process to explain progression to hepatocellular damage, inflammation and fibrosis [3,4]. Several clinical studies of NAFLD have demonstrated that an injurious oxidative process is operating. The cytotoxic products of lipid peroxidation, 4-hydroxy-2′-nonenal and malondialdehyde, were preferentially detected in liver from patients with NAFLD (but not in normal livers) and their indices correlated with both necroinflammatory grade and fibrosis stage [5,6]. Sanyal et al. [7] reported a similar observation using 3-nitrotyrosine as a marker for lipid peroxidation. 8-Hydroxydeoxyguanosine, a DNA-base-modified product generated by free radicals, has been shown in over 60% of livers from patients with NASH, but rarely in fatty liver, and it was absent from control liver [5]. Likewise, Videla et al. [8] in this issue of Clinical Science have confirmed that (morbidly) overweight patients with NAFLD exhibit a substantial pro-oxidant pattern in the liver, as shown by higher protein carbonyl content and systemic oxidant stress.

Conceptually, oxidative stress results from a change in the equilibrium between production of pro-oxidant and their consumption or deactivation, favouring an excess of pro-oxidant that may have noxious consequences at the molecular, cellular and tissue level. To date, most of the effort to understand the mechanisms of oxidative stress in NAFLD has been focused on generation of pro-oxidants. Several potential sources have been proposed, such as mitochondrial release of reactive oxygen species [9–11], induction of microsomal cytochrome P450 (CYP) [4], peroxisomal production of hydroperoxide [11,12] or the inflammatory process itself. Cytochrome P450 and, in

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particular, CYP2E1, characterized as a free enzyme with high pro-oxidant activity, is a potential source of oxidative stress in NASH [4]. Up-regulation of CYP2E1 has been reported in NASH livers [13], and a positive association between the degree of steatosis and CYP2E1 activity, as measured by in vivo metabolism of a probe drug, has been observed in morbidly obese patients [14]. However, there was no analysis of the degree of CYP2E1 expression and the severity of inflammation in NAFLD. In this issue of Clinical Science, Videla et al. [8] directly measured protein expression and CYP2E1 activity on liver samples and confirmed the hepatic induction of this enzyme. Interestingly, CYP2E1 hepatic protein and activity were higher in livers from patients with steatohepatitis than in those with uncomplicated steatosis [8]. This observation suggests that further CYP2E1 induction could be related to the progression from steatosis to steatohepatitis.

The liver is richly endowed with antioxidant defence mechanisms. These are integrated in all cell compartments and are equipped with the capacity and adaptability to counter massive changes in production of pro-oxidants. To date, the literature provides little data regarding the antioxidant status in NAFLD. Videla et al. [8] report for the first time that NAFLD/NASH in overweight patients was associated with hepatic glutathione (GSH) depletion. Whether due to nutritional depletion, excess consumption or a defect in its recycling, lowered GSH potentially predisposes cells to oxidant stress, even without excessive generation of pro-oxidants. It is also salient to note that, in humans, alcohol-induced steatohepatitis as well as florid steatohepatitis secondary to gastro-jejunal bypass are associated with nutritional depletion and lowered GSH levels.

In addition to GSH, hepatic superoxide dismutase (SOD) activity was also decreased [8]. This indicates a more profound derangement in the hepatic antioxidant status, which is accompanied by systemic evidence of oxidative stress in the form of diminished total antioxidant capacity of plasma. In the subgroup of patients with NASH, Videla et al. [8] have shown that the hepatic antioxidant defences were reduced further, as indicated by a more global inhibition of SOD, catalase and glutathione peroxidase activities, leaving the hepatocyte with little resistance towards attacks by pro-oxidants. The authors [8] suggest that the decreased efficiency of antioxidant systems could be the direct consequence of oxidative stress. However, this view could be questioned. Indeed, increased GSH synthesis and induction of antioxidant enzymes are common findings in studies of differential gene expression induced by pro-oxidants [15] and these are believed to be the physiological regulatory response to increased pro-oxidants in an attempt to prevent or combat oxidative injury. This phenomenon has also been demonstrated in CYP2E1-transfected cells that are chronically exposed to increased production of reactive oxygen species [16]. Furthermore, Type II diabetes is associated with reduced hepatic expression of SOD [17] and, recently, Sreekumar et al. [18] have shown a transcriptional down-regulation of antioxidant enzymes in cirrhosis secondary to NASH when compared with healthy controls and cirrhosis of other origins. Although this end-stage liver disease might not reflect the situation encountered in less advanced NAFLD, these observations raise the hypothesis that decreased activity of the antioxidant systems might represent an ‘inadequate response’ of pathological significance in NAFLD.

In conclusion, the study by Videla et al. [8] illustrates elegantly that NAFLD is associated with impaired antioxidant pathways, which are more severe in steatohepatitis than in uncomplicated fatty liver. These interesting data obviously need to be confirmed in larger populations and to be correlated with resulting oxidative stress and hepatic injury. Longitudinal studies with repeated biopsies in patients with progressive and non-progressive NAFLD could also help to elucidate whether decreased activity of antioxidant systems is a bystander of disease progression, or whether it favours or determines a pejorative evolution. Indeed, altered efficiency of antioxidant pathways could be constitutive or pre-existing to NAFLD. Early detection of such a defect might help to identify subpopulations more sensitive to pro-oxidants and at higher risk of developing progressive inflammatory and fibrosing NASH to which prevention and therapeutic efforts should be concentrated.

REFERENCES


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