

Alcoholic liver disease, oxidative stress, and antioxidants

Excessive alcohol consumption is a major public health issue in today's society. Alcohol is estimated to cause nearly 195,000 deaths every year in the European Union (1). In Spain, 17,278 alcohol-related deaths occurred in 2006, which represents 4.6% of total deaths (2). In addition to being a drug that may induce dependence, alcohol is a toxic substance that may harm all organs and systems in the body, and up to about 60 diseases have been described including mental and behavioral disorders, cancer, cardiovascular disease, lung disorders, and liver diseases. Excessive alcohol intake long-term may result in liver damage. Liver lesions are progressive, and characterized by various disease stages. The initial lesion seen in excessive alcohol use is liver steatosis, which is present in 90% of alcohol consumers (3). The next stage is alcoholic hepatitis, characterized by inflammation, necrosis, and liver cell apoptosis, as well as an increase in liver enzymes such as alanine aminotransferase and aspartate aminotransferase. The clinical spectrum of alcoholic hepatitis may vary from asymptomatic subjects with moderately elevated transaminases to severe liver dysfunction with serious complications such as jaundice, liver encephalopathy, ascites, esophageal varices, coagulopathy, and coma. Both steatosis and moderate alcoholic hepatitis may be reversed upon alcohol cessation. In contrast, severe alcoholic hepatitis results in a mortality rate of 30-60%. Lastly, approximately one half of patients with alcohol-related hepatitis will progress to a final stage of cirrhosis, characterized by, regeneration nodules, and loss of liver sinusoids (3). Alcoholic cirrhosis is presently a common indication for liver transplant worldwide.

Despite advances in the understanding of alcohol metabolism, the mechanisms of hepatocellular damage remain unclear (4). One of the mechanisms drawing greater interest among the scientific community is the role of oxygen free radicals in alcohol-mediated liver toxicity. Over 10,000 scientific papers on oxidative stress were published last year, which illustrates the growing interest in this field. Under certain conditions, including acute or chronic alcohol exposure, oxygen free radical generation increases and antioxidant levels decrease. The result is the so-called oxidative stress, characterized by a disbalance between free radical production and cell defense systems (5). Oxygen free radicals include a variety of reactive species such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH). These species are highly unstable because their molecules exhibit unpaired electrons that react with other atoms and molecules to give rise to stable compounds (5). Oxidative stress induces hepatocyte necrosis and apoptosis. Similarly, oxygen free radicals enhance lipoperoxidation, which induces inflammation and fibrosis. Furthermore, patients with alcoholic cirrhosis have decreased reduced glutathione (GSH) and vitamin E levels in the liver (6).

While the impact of alcohol on the liver has been extensively studied, experimental and clinical research on its effects regarding functional impairment in other organs is

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equally as relevant, and opens up new perspectives for translational investigation in the field of oxidative stress. In this regard, alcohol consumption induces significant changes in gastrointestinal tract cells. Alcohol causes necrotic lesions in the gastric mucosa, reduces gastric mucus and bicarbonate secretion, and impairs permeability (7). Thus, a significant alcohol-induced decrease has been demonstrated in the activity of antioxidant enzymes catalase, superoxide dismutase, and glutathione peroxidase in the gastric and intestinal mucosa of rats. Antioxidant activity and gastrointestinal tract function recover by the ingestion of compounds with antioxidant properties (7). In addition to changes in the gastrointestinal mucosa, long-term alcohol ingestion also impairs the gastrointestinal neuromuscular system. Ethanol has been seen to reduce gastrointestinal contractility and Oddi's sphincter motility by inhibiting calcium from entering gastrointestinal muscle fibers (8,9). Of late, oxidative stress was recognized as a relevant factor contributing to intestinal dysmotility in postoperative ileus (10) and diabetic gastroparesis (11). This issue of *Revista Española de Enfermedades Digestivas* includes an interesting paper by the team at Physiology Department, Saragossa University Veterinary School (12), which demonstrates that ethanol reduces the amplitude of both spontaneous and acetylcholine-induced contractions in the duodenal muscle layer of rabbits in association with increased lipoperoxidation in *ex vivo* studies. The study reveals that intestinal motility changes are a response to ethanol-induced oxidative stress. In an effort to limit alcohol effects, the authors have shown that trolox, a hydrophilic analogue of the classic antioxidant vitamin E, antagonized the ethanol-induced inhibition of acetylcholine-induced contractions in the longitudinal and circular muscle layers. Trolox also reduced ethanol-associated oxidative stress as reflected by a decrease in lipoperoxidation byproducts (malondialdehyde or MDA). Further studies are no doubt needed along the lines of the data provided by this paper regarding oxidative stress-related gastrointestinal motility changes during alcohol-induced acute and chronic conditions, and their treatment with antioxidant drugs.

The use of antioxidants in clinical practice has been highly controversial. In a recent systematic review on antioxidant supplementation for liver conditions, including alcohol damage, no convincing evidence was found for the benefits of antioxidants such as β -carotene, vitamins A, C, E, and selenium in the management of said conditions (13). However, trial included for review were of poor quality, and the risk for systematic errors was high. Similarly, a review of 9 randomized clinical trials also found no evidence to support or refute the use of S-adenosylmethionine (SAM) in alcoholic liver disease (14). In contrast, there is experimental evidence for the liver-protecting role of antioxidants such as SAM (15) or melatonin (16) for alcoholic liver disease and experimental cholestasis. While waiting for results from well-designed clinical trials to recommend antioxidants would be scientifically appropriate, experimental evidence may support their administration at least in controlled regimens.

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