Oxidative Stress Management in Pre-Cancer

Subjects: Oncology

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Chronic viral hepatitis B and C and non-alcoholic fatty liver disease (NAFLD) have been widely acknowledged to be the leading causes of liver cirrhosis and hepatocellular carcinoma. As anti-viral treatment progresses, the impact of NAFLD is increasing. NAFLD can coexist with chronic viral hepatitis and exacerbate its progression. Oxidative stress has been recognized as a chronic liver disease progression-related and cancer-initiating stress response. However, there are still many unresolved issues concerning oxidative stress, such as the correlation between the natural history of the disease and promising treatment protocols. Recent findings indicate that oxidative stress is also an anti-cancer response that is necessary to kill cancer cells. Oxidative stress might therefore be a cancer-initiating response that should be down regulated in the pre-cancerous stage in patients with risk factors for cancer, while it is an anti-cancer cell response that should not be down regulated in the post-cancerous stage, especially in patients using anti-cancer agents. Antioxidant nutrients should be administered carefully according to the patients' disease status.

Keywords: oxidative stress ; chronic hepatitis ; hepatocellular carcinoma ; antioxidant

1. Introduction

Given that oxidative stress is involved in chronic viral hepatitis and NAFLD cross-sectional pathology, the management strategy can be commonly applied. Nutritional support or supplementation is used to eliminate ROS or activate antioxidant pathways, such as the Nrf2 pathway[1]. In the case of the simultaneous activation of Nrf2 and NFkB, Nrf2 acts antagonistically against NFkB[2]. In a chemically induced liver fibrosis model, antioxidant pomegranate juice, which contained anthocyanins and hydrolysable tannins, reduced hepatic fibrosis via Nrf2 activation and NFkB inactivation[3]. Adjusting for the balance of inflammatory or oxidative stress responses and the antioxidant response in the presence of disease according to the patient's oxidative stress condition is necessary; however, at present, this approach is not widely applied. The difficulty in defining the oxidative stress status is one reason for this. This background probably explains why the results of clinical studies of antioxidants to regulate carcinogenesis are often unsuccessful.

Trace elements are involved in oxidative stress-related conditions. Some of them, such as iron and zinc, are able to be measured as standard clinical markers and monitored. Iron has been shown to be toxic as an oxidative stress inducer in chronic liver disease, as mentioned in Section 2.4, and its level can be reduced by phlebotomy or iron chelator administration in chronic hepatitis and NASH[4]. Zinc plays a role in the reduction of inflammatory cytokines and oxidative stress via the synthesis of antioxidant enzymes and catalyzing enzymes, or by influencing transcriptional factors[5]. One of the inflammation related transcription factors NF-κB is reduced via its negative regulator zinc finger protein (A20) or PPAR-αα. An antioxidant enzyme Cu,Zn- SOD (SOD1) contains zinc as a co-factor. Zinc has been shown to be deficient in cases of chronic liver disease, especially cirrhosis, possibly because of the impaired absorption from the intestine and increased excretion in the urine[6]. Zinc is necessary for the function of Paneth cells, which prevent pathogenic microbial invasion in the intestine, a risk for subsequent hepatic inflammation via α-defensin production[7]. However, the presence of excess dietary zinc increases oxidative stress with an increased intestinal permeability that should be avoided[8]. An appropriate and effective supplementation strategy is therefore necessary, even for trace elements.

Selenium is one of the essential elements required for the normal development of human and animal organisms. Selenium activates GPx, which is a representative antioxidant enzyme. The Gpx-1 enzyme activity and mRNA levels decrease dramatically in a selenium deficient diet, whereas other selenoproteins are less sensitive[9]. Feeding a selenium deficient diet with glutathione deficiency resulted in oxidative stress, during which the protein malondialdehyde levels increase in the liver and an individual thus becomes sensitive to drug induced liver injury, thereby indicating the necessity of selenium for antioxidant system activation[10]. Given that the blood selenium level was observed to decrease in liver cirrhosis patients, supplementation may be one approach to improve the antioxidant function in such cases[11].

2. Dietary Intervention for Oxidative Stress

The potential dietary antioxidant intake has been assessed in several studies. Even an increase in the food frequency questionnaire-defined dietary total antioxidant capacity was shown to be correlated with a lower liver histological assessment of NASH-related hepatocellular ballooning[12]. The intake of orange juice, a source of flavonoids and vitamin C, for eight weeks, resulted in a reduction of total cholesterol, LDL-cholesterol, C reactive protein, and oxidative stress related markers, in a randomized study of 43 chronic hepatitis C patients [13]. Dietary vitamin C intake was shown to be inversely correlated with the presence of NAFLD, similarly to vitamin E, suggesting the favorable effect of both vitamins[14]. The positive effect of the intake of vitamin C on NAFLD prevention was shown to be dominant in middle-aged, non-obese males[15].

An iron-reduced diet, often coupled with phlebotomy, has been shown to be effective against chronic hepatitis C and NASH, resulting in a reduction of the risk of hepatocarcinogenesis[16]. Zinc supplementation has been evaluated in more than 1300 studies, although not many have shown statistically significant favorable results[17].

A small number of studies showed the preferable effects of zinc supplementation, suggesting the important role for antioxidant response. The transaminase level in chronic hepatitis C patients decreased[18], and the serum levels of type IV collagen and tissue inhibitors of matrix-metalloproteinase-1 (TIMP-1) levels in chronic hepatitis patients also decreased[19]. In cirrhosis patients, zinc supplementation may help to improve protein catabolism[20]. As zinc is often involved in standard laboratory examinations, to measure, evaluate, and adequate supplementation are thus all necessary steps. Large scale studies defining the best approach in chronic liver diseases are thus called for in the future.

Selenium supplementation has been shown to be effective in some patients with chronic thyroiditis, due to its immune targeting effect[21]. During chemotherapy for cancer patients, selenium supplementation has been shown to be associated with an improvement in fatigue, as well as in the liver and renal function[22]. However, in primary biliary cirrhosis, the supplementation of selenium did not show any antioxidant activities, while the renal excretion was increased, suggesting that a cirrhotic liver could not take advantage of selenium adequately[23]. Although selenium administration helps in the recovery of hepatic steatosis via PPAR-α activation in some diabetic mouse models[24], selenium supplementation to humans has been cautioned to increase the risk of type 2 diabetes[25]. It therefore remains difficult to draw any definite conclusions about selenium supplementation as an antioxidant.

3. Clinical Trials for Oxidative Stress

Many clinical trials have been undertaken to investigate whether antioxidants prevent cancer or death; however, the results are confusing. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), alpha-tocopherol reduced the incidence of prostate cancer, whereas beta-carotene increased the incidence of lung cancer and total mortality[26]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized control trial (RCT) that aimed to show the potential for vitamin E to reduce the risk of prostate cancer, showed a 17% increase in the incidence of prostate cancer[27]. Another study showed that beta-carotene supplementation was associated with an increased risk of lung cancer[28]. An epidemiologic study showed that dietary vitamin E intake and vitamin E supplement use was associated with a reduced risk of liver cancer, although vitamin C and multivitamin intake increased the risk of liver cancer[29]. To define the real effect of antioxidant supplementation, studies should be planned according to the oxidative stress-related conditions before the start of intervention.

Antioxidant therapy, such as the administration of vitamin E, has been shown to be effective in improving inflammation and histological activity in NASH and is recommended in several guidelines for NAFLD. However, the long-term effect of these therapies, including the beneficial effects on the risk of hepatocarcinogenesis, is unclear[30][31]. There are also other antioxidant agents that have been shown to have favorable effects on NASH and NASH-related hepatocarcinogenesis.

Antidiabetic agents are recommended for NAFLD patients complicated with diabetes. Most of the antidiabetic agents, but not insulin or insulin producers, have been shown to be effective for NAFLD. Metformin and pioglitazone have been accepted as representative antioxidant agents[32]. Metformin has also been shown to activate AMPK by inhibiting mitochondrial complex I and inducing AMPK-independent lysosomal changes, resulting in many favorable effects in carcinogenesis and the post-carcinogenesis control of cancers[33]. Metformin-related AMPK pathway activation is involved in many cell types, including T cells, B cells, hepatocytes, and even liver fibrosis-inducing hepatic stellate cells (HSCs). As an antioxidant agent, metformin activates the Nrf2 signaling pathway, resulting in the production of heme oxygenase-1 (HO-1; an antioxidant enzyme), in human endothelial cells and thereby increasing the antioxidant function of these cells. However, in several cancer cell lines, including HCC, metformin suppressed the Nrf2 expression in an AMPK-independent

manner[34]. Research on the effect of metformin on normal and cancerous cells is still ongoing. At present, this agent is recognized as suitable for pre-cancer administration, to prevent hepatocarcinogenesis and post-cancer administration, to prevent HCC recurrence.

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that play key roles in cellular metabolic homeostasis and inflammation. Pioglitazone is a diabetes agent that activates PPAR-g. It has been shown to improve insulin resistance, and several studies reported a favorable effect on NASH. One six-month randomized study of pioglitazone plus hypocaloric diet showed a plasma aminotransferase decrease, insulin sensitivity improvement, hepatic fat content decrease, and a histopathological reduction in liver necro-inflammation[35]. However, an additional analysis of select patients in the same cohort revealed that pioglitazone induced whole-body weight gain, and the increased weight was due to an increase in adipose tissue mass and not water retention [36].

Other antioxidants have been shown to be effective in several small series of studies. The administration of L-carnitine (a mitochondrial long-chain fatty acid uptake-related molecule) was reported to be associated with the histological improvement of NASH in a mouse model[37] and an RCT[38] . Flavonoids (heterogeneous polyphenols) have been shown to exert an antioxidant function, protecting the liver in a CCl_4-induced liver injury model[39]. A mixture of flavonolignans and minor polyphenolic compounds derived from the milk thistle plant (*Silybum marianum*) named silymarin has been shown to have antioxidant power [40]. The main component of silymarin, silybin, has been shown to restore nicotinamide adenine dinucleotide (NAD+) levels, decreasing the glucose uptake and lipid peroxidation and resulting in the improvement of NAFLD[41][42]. Silymarin was shown to be effective for improving NASH-related fibrosis in a randomized, double-blind, placebo-controlled study, although the number of patients was relatively small (49 for silymarin and 50 for placebo)[43] .

Many studies using antioxidant agents have shown promising results for NAFLD, suggesting that these agents may be viable candidate compounds in addition to standard vitamin E.

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