Beneficial effect of refined red palm oil on lipid peroxidation and monocyte tissue factor in HCV-related liver disease: a randomized controlled study

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BACKGROUND: A large amount of endotoxin can be detected in the peripheral venous blood of patients with liver cirrhosis, contributing to the pathogenesis of hepatotoxicity because of its role in oxidative stress. The present study aimed to test the effect of the supplementation with red palm oil (RPO), which is a natural oil obtained from oil palm fruit (*Elaeis guineensis*) rich in natural fat-soluble tocopherols, tocotrienols and carotenoids, on lipid peroxidation and endotoxemia with plasma endotoxin-inactivating capacity, proinflammatory cytokines profile, and monocyte tissue factor in patients with chronic liver disease.

METHODS: The study group consisted of sixty patients (34 males and 26 females; mean age 62 years, range 54-75) with Child A/B, genotype 1 HCV-related cirrhosis without a history of ethanol consumption, randomly enrolled into an 8-week oral daily treatment with either vitamin E or RPO. All patients had undergone an upper gastrointestinal endoscopy 8 months before, and 13 out of them showed esophageal varices.

RESULTS: Both treatments significantly decreased erythrocyte malondialdehyde and urinary isoprostane output, only RPO significantly affected macrophage-colony stimulating factor and monocyte tissue factor. Liver ultrasound imaging did not show any change.

CONCLUSIONS: RPO beneficially modulates oxidative stress and, not least, downregulates macrophage/monocyte inflammatory parameters. RPO can be safely advised as a valuable nutritional implementation tool in the management of chronic liver diseases.

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KEY WORDS: endotoxin; isoprostane; macrophage-colony stimulating factor; monocyte tissue factor; oxidative stress; red palm oil

Introduction

Several studies[1-3] have described that a large amount of endotoxin can be detected in the peripheral venous blood of patients with liver cirrhosis. Once absorbed, endotoxin by promoting a reactive neutrophil migration to the liver and by activating the resident macrophage population, further contributes to the pathogenesis of hepatotoxicity.[4-6] A recent study[7] on patients with liver cirrhosis have shown that the independent and strongest factors for predicting hepatic venous pressure gradient and hepatic sinusoid resistance are plasma levels of nitric oxide, malondialdehyde (MDA), and endotoxin. On the other hand, the relationship between clotting activation and endotoxemia has been investigated by measuring the expression of monocyte tissue factor (TF).

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Indeed, it has been found that cirrhotic patients have an enhanced monocyte TF expression that correlated significantly with endotoxemia.[8] In patients with liver cirrhosis complicated by encephalopathy, the administration of disaccharides, by modifying the gut ecosystem and intestinal transit time, represents the most common therapeutic strategy aimed to lower the gut absorption of toxic products such as mercaptans, endotoxin, organic acid, etc.[9, 10] However, such kind of intervention has no beneficial influence whatsoever on the redox balance and inflammatory responses in these patients who have been shown to have a detrimental profile, either for vitamin E deficiency and for intrinsic disease mechanism.[11] Intestinal mucosa alterations have been reported at the subcellular level, in relation to an increased oxidative stress taking place in experimental liver cirrhosis.[12] In the present study we investigated the isoprostane-F2α-III which is one of the most abundant F2-isoprostanes formed under physiological conditions in humans. It is generated during low density lipoprotein oxidation and its urinary excretion represents the most reliable and clinically relevant marker of global oxidative stress *in vivo* in humans.[13, 14] Devaraj et al[15] has demonstrated that after vitamin E supplementation monocyte formation of oxidant species, lipid oxidation and interleukin-1β secretion were significantly decreased. Since there is report warning against the use of antioxidant resveratrol in HCV patients,[16] we studied if a whole nutrient-based approach would bring about beneficial effect. In this setting, we used red palm oil (RPO) which is a natural oil obtained from oil palm fruit (*Elaeis guineensis*) rich in natural fat-soluble tocopherols, tocotrienols and carotenoids, which act as potent antioxidants. In particular, tocotrienol-rich fraction of palm oil consists of three distinct isoforms of tocotrienols (α, γ and δ) as well as α-tocopherol and while these isomers possess comparable antioxidant properties, their abilities to potentiate signal transduction is likely to be different and synergizing. Indeed, despite the high saturated fat content of RPO, studies[17, 18] have demonstrated that RPO is associated with better recovery and protection of oxygen-susceptible cells such as cardiomyocytes and spermatozoa when exposed to oxidative stress. The present study was to test the effect of tocopherol/tocotrienol-rich palm oil on lipid peroxidation and endotoxemia with plasma endotoxin-inactivating capacity, proinflammatory cytokines profile and monocyte TF in patients with chronic liver disease.

Methods

The study group consisted of sixty patients (34 males and 26 females, with a mean age of 62 years, range 54-75) with Child A/B, genotype 1 HCV-related cirrhosis without having a history of alcohol consumption for the past 10 years. In our study we did not have any placebo group, because making a placebo of RPO would have provided them some colored fatty oil and this was not regarded as ethical by the ethics committee of the institution.

All patients had abnormal ALT levels but less than two-fold upper normal limits. We purposely chose those patients with low grade on-going hepatic damage activity since we were not aware of the outcome of the study, and also because those with high aminotransferases levels were under study for interferon treatment, and the institutional ethics committee would not have approved it.

The patients were carefully interviewed with special attention to their dietary-vitamin using a standardized food-composition table.[19] Exclusion criteria included hemochromatosis, Wilson's disease, α-1-antitrypsin deficiency, autoimmune diseases, alcohol consumption, hepatocellular carcinoma, recent variceal hemorrhage or scheduled endoscopic session of variceal banding, any other malignancy, chronic illness requiring steroids, immunosuppressive agents, allopurinol treatment, antiviral or NSAIDs, concomitant use of vitamin/food supplements, strenuous physical exercise, chronic renal failure, arterial hypertension, overt cardio-respiratory abnormality and high consumption of caffeine-containing food or beverages. There was no history of recent treatment with antibiotics, laxatives or disaccharides. At entry there was no evidence of any infectious or inflammatory diseases.

All patients had undergone an upper gastrointestinal endoscopy 8 months before, and 13 out of them showed esophageal varices. Three patients were under treatment with ursodeoxycholic acid, 19 with potassium-sparing diuretics, and 4 had courses of furosemide. In particular, all patients at the entry or the end of the study were studied by liver ultrasound by one skilled radiologist. Fifteen healthy teetotallers were considered as a control group, matched for age and gender with the study group and met the exclusion criteria.

Written consent was obtained from all patients before the study and the study conforms to the ethics guidelines of the 1975 *Declaration of Helsinki*; in addition, the procedures have been approved by the intitutional ethics committee.

Study design

After an overnight fasting, the patients and controls had blood samples withdrawn to measure: routine blood chemistry and other variables as below. All cirrhotic patients were then randomly enrolled into an 8-week oral daily treatment with either: A) 28 patients (14 males/14