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Circulating markers of oxidative stress and liver fibrosis in Sudanese subjects at risk of schistosomiasis and hepatitis

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Abstract

Epidemiological studies in the developing world are frequently biased by the simultaneous presence of several infectious pathogens. In the present study, we examined the usefulness of circulating markers of oxidative stress and liver fibrosis to investigate the distinct forms of chronic liver inflammations associated with schistosomiasis and viral hepatitis, respectively. The study was performed in a Sudanese population exposed to *Schistosoma*. Circulating hyaluronic acid (HA) was used as a marker of liver fibrosis; the severity of schistosomiasis was determined by ultrasonic examination; viral hepatitis infection was ascertained by circulating anti-hepatitis antibodies. Serum markers were examined also in Sudanese subjects not exposed to *Schistosoma* infection and in French control subjects. We found a drastic decrease of lycopene levels in the subjects exposed to schistosomiasis in comparison with non-exposed Sudanese and French control subjects. Retinol, α-tocopherol and five carotenoids were unchanged. Lycopene depletion was unlikely to be due to variations of nutritional origin, since the lycopene/β-carotene ratio was five-fold lower in the population at risk of schistosomiasis than in the other groups. We found that high HA serum levels were associated with severe periportal fibrosis but not with viral infection. Conversely, levels of the oxidized lipid malondialdehyde (MDA) were associated with viral infection but not with the severity of schistosomiasis, even though the two infections had additive effects. We concluded that serum markers are valuable tools for investigating the complex effects of co-existing factors of chronic liver inflammation.

Keywords: Liver fibrosis; Malondialdehyde; Hyaluronate; Hepatitis; *Schistosoma mansoni*

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1. Introduction

People in developing countries, especially in Africa, suffer disastrous sanitary conditions with a high prevalence of chronic infections, such as HIV, viral hepatitis, tuberculosis and those due to parasites. Under these conditions, infections with several pathogens are usual. Therefore, field investigations face the challenge of coping with such a complex situation while employing user-friendly techniques, such as blood marker exploration and portable examination equipment. Along these lines, we examined Sudanese subjects with co-existing *Schistosoma* and viral hepatitis infections. The two diseases are often associated in developing countries (Halim et al., 1999) and both lead to chronic liver inflammation.

The study focuses on blood parameters associated with chronic oxidative stress as reactive oxygen species (ROS) play a central pathophysiological role in both infections. Plasma concentrations of anti-oxidant liposoluble vitamins and carotenoids are known to decrease in patients with chronic viral hepatitis (Newsome et al., 2000; Rocchi et al., 2001). There is an inverse relationship between serum anti-oxidants and viral disease progression (Evans and Halliwell, 2001; Tang et al., 1997; Yadav et al., 2002). The main ROS targets are membrane lipids, which upon oxidation form lipid peroxides (LPO), usually referred to as thiobarbituric acid-reactive substances (TBARS). The lipid peroxidation product malondialdehyde (MDA) is of particular usefulness for the clinical management of patients suffering from chronic viral hepatitis since its plasma concentration correlates with disease severity (De Maria et al., 1996; Romero et al., 1998). ROS and lipid peroxidation products initiate a fibrogenesis cascade with overexpression of fibrogenic cytokines and increased gene transcription and synthesis of collagen (Houglum et al., 1997; Poli and Parola, 1997). It has been shown that the occurrence of MDA adducts correlates positively with fibrosis in hepatitis C patients (Paradis et al., 1997). The degree of hepatic fibrosis can be evaluated using serum hyaluronic acid (HA) concentration (Oberti et al., 1997), which is predictive for the occurrence of severe complications in HCV cirrhosis (Guechot et al., 2000).

Regarding *S. mansoni* infection, ROS are produced in the immediate vicinity of eggs deposited in the liver (Abdallahi et al., 1999) and lead to the destruction of the eggs (Hanna et al., in press). However, ROS have devastating side effects since liver redox homeostasis is altered with a decrease in the anti-oxidant defences of the organ (Gharib et al., 1999; La Flamme et al., 2001). In man, infection with *S. mansoni* is associated with increased levels of circulating TBARS and ROS adducts (Pascal et al., 2000). The resulting fibrosis is concentrated in portal blood vessels, leading to unique form of fibrosis, the pipestem Symmers' fibrosis, distinct from that associated with viral infection.

In other parasitic diseases, such as malaria, circulating levels of α-tocopherol, retinol and of several carotenoids were shown to be lower in patients than in control subjects (Das et al., 1996; Metzger et al., 2001). Data suggest an increased utilization of Vitamin A in acute-phase Thai patients, after making allowance for the fact that parasitic diseases co-exist with malnutrition in many places (Thurnham and Singkamani, 1991). However, the relationship between parasitic infection and carotenoid status depends on multiple factors, in particular the parasite involved and the immune status of the patients. Malaria, but not urinary schistosomiasis or infection with intestinal parasites, was associated with low retinol levels (Sturchler et al., 1987). However, malarial parasitemia may contribute to low serum retinol levels in non-immune preschool children but not in semi-immune primary school ones (Friis et al., 1997). Nevertheless, it has been suggested that retinol may form part of the normal host defense against malaria and contribute directly to parasite clearance (Davis et al., 1998). The protective effect of retinol might be exerted through the enhancement of the Th2 response (Stephensen et al., 2002) and the reduction of proinflammatory cytokine production (Serghides and Kain, 2002).

However, it must be pointed out that, with respect to their radical scavenging properties and their specific distribution in the body, not all diet-derived anti-oxidants have the same physiological importance. For example, recent studies employing biomarkers of oxidative DNA damage question the anti-oxidant role of β-carotene and ascorbate (Halliwell, 1999). Furthermore, administration of anti-oxidants may either protect against or increase damage, depending on the pathophysiological context (Halliwell, 2000). Also, there is an optimal level of protection for each carotenoid (Stahl and Sies, 2002). Thus, the role of diet-derived anti-oxidants in disease development and