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Hepatic Oxidative Stress: Role of Liver Biopsy

Mahmoud Rushdi Abd Ellah
Department of Animal Medicine,
Faculty of Veterinary Medicine, Assiut University,
Assiut Egypt

1. Introduction

Free radicals are highly reactive substances produced continuously during metabolic processes. They participate mainly in physiological events such as the immune response, metabolism of unsaturated fatty acids, and inflammatory reaction. The balance between free radicals and antioxidants is disrupted in many diseases. This disruption may be attributed to a number of factors such as the inability of the cells to produce sufficient amounts of antioxidants, the nutritional deficiency of minerals or vitamins, and the excess production of reactive oxygen species (Abd Ellah, 2010). Free radical excess results in impairment of DNA, enzymes, and membranes and induces changes in the activity of the immune system and in the structure of basic biopolymers which, in turn, may be related to mutagenesis and aging processes (Poli, 1993).

The involvement of oxidative stress in the pathogenesis of hepatic dysfunction in human (Comporti, 1998; Poli et al.,1987; Zern et al., 1990; Poli, 1993; Tsai et al., 1993; De Maria et al., 1996; Gonzalez-Correa et al., 1997; Paradis et al., 1997; Feher et al., 1998; Wallace & Miller, 2000; Spirli et al., 2001; Alpini et al., 2002; Cesaratto et al., 2004; Jabłonowska et al., 2005) and animals (Khan et al., 1987; Mudroň et al., 1997; 1999; Spolarics, 1999; Sansinanea et al., 2000; Abd Ellah et al., 2002; 2004, 2007, 2008, 2009, 2010) has been investigated for many years.

Some of the liver diseases were associated with increase (Farinati et al., 1995; Abd Ellah et al., 2002, 2008) or decrease (Mudroň et al., 1997; Barbaro et al., 1999; Abd Ellah et al., 2004; Videla et al., 2004; Czeczot et al., 2006) antioxidants contents. Usually hepatic antioxidants increased at the beginning of hepatic disease and decreased in severe hepatic injury. The advantages of measuring hepatic oxidative status in liver biopsy are that it helps in diagnosis of hepatic dysfunction, reflects the degree of deterioration in the liver tissues, and helps to determine the severity of hepatic injury, and also, aid in recommending antioxidant's therapy in patients that had a hepatic disease with derangement in hepatic antioxidant constituents. The main purpose of the current article is to explore the value of liver biopsy as a tool for detection of hepatic oxidative stress. A focus was done on different types of free radicals, antioxidants, lipid peroxidation, and hepatic and blood oxidative status in hepatic dysfunction.

2. Free radicals

2.1 Types of free radicals

Free radicals can be defined as molecules containing a single unpaired electron in atomic or molecular orbits. These molecules have an important role in the pathogenesis of tissue

damage in various disorders (Dalgic et al., 2005), such as hepatic dysfunction, mastitis, kidney damage, inflammation, immune injury and carcinogenesis (Abd Ellah, 2010). The most important free radicals include superoxide anion ($O_2 \cdot^-$), hydroxyl radical ($\cdot OH$), and hypochlorous acid (HOCL) (Stohs, 1995). HOCL is produced by the reaction of hydrogen peroxide (H_2O_2) with chloride ions and plays an important role in the leukocyte respiratory burst, which is involved in the host defense system (Lunec, 1990). Nitric oxide ($NO\cdot$) acts as a free radical and as a biological mediator in biochemical reactions. Physiologically it is synthesized from L-arginine by NO synthase employing cofactor NADPH. In the host, $NO\cdot$ arises in some pathological situations, such as sepsis, stroke, myocardial depression, and inflammatory responses (Bredt & Snyder, 1994).

Superoxide anion induces important reducing reactions in biological materials via Fenton-like reactions, which are catalyzed by redox cycling metal ions, including iron, copper, chromium and vanadium (Stohs & Bagchi, 1995). These metal ions have the ability to accept and donate single electrons, making them important catalysts of free radical reactions, the most widely distributed and most commonly studied transition metal ions are the cations iron and copper (Stohs, 1995). Superoxide anion reduces Fe^{3+} in metalloproteins such as ferritin. The reduction of protein bound iron is an important reaction in biological material, because if there is sufficient H_2O_2 available, a reaction between the resultant Fe^{2+} and H_2O_2 occurs and gives rise to the highly reactive $\cdot OH$ (Lunec, 1990). H_2O_2 traverses biological membranes and intracellularly targets phospholipids, carbohydrates, metalloproteins and DNA, and causes damage via Fenton's reaction (Samuni et al., 1981).

2.2 Sources of free radicals

Free radicals may be released in the liver as a subsequence to hepatic detoxification of drugs, chemicals and toxic materials (Feher et al., 1992; Ogino & Okada, 1995). The formation of oxygen free radicals may be physiological as in phagocytosis (superoxide and H_2O_2 are used by phagocytic cells to kill bacteria), a side effect of metabolic pathways, or may occur in pathological conditions due to toxic agents as in the case of ischemia, inflammation, disease, or due to decreased antioxidant defenses (Miller et al., 1993).

Mitochondria considered a major source for the production of $O_2\cdot^-$ and H_2O_2, about 2-3% of consumed oxygen is constantly converted into reactive oxygen/reactive nitrogen species (ROS/RNS) in the mitochondria, hepatocytes contain many mitochondria and therefore, generate excess ROS/RNS (Stohs, 1995).

In many liver diseases, including the wide range of neonatal hepatitis, the tissue inflammatory infiltrates are likely to be responsible for the formation of $O_2\cdot^-$, H_2O_2, $\cdot OH$, HOCL and the highly cytotoxic monochloramine (Southorn & Powis, 1988; McCord, 1993). In turn, the superoxide anion attracts further neutrophils to the inflammatory site by a chemotactic activity, causing an increase in tissue injury (Petrone et al., 1980). In addition, activated macrophages, Kupffer cells and vascular endothelium can generate nitric oxide, which may react with superoxide generating peroxynitrite. The latter is responsible for the inhibition of mitochondrial respiration and DNA synthesis (Moncada & Higgs, 1993).

Liver damage due to iron (hemochromatosis) and copper overload is believed, at least partially, to derive from the catalytic activity of these metals in the Fenton reaction leading to the generation of ROS and increased lipid peroxidation with consequent abnormal mitochondrial function (Bacon et al., 1993; Sokol et al., 1993; Sokol et al., 1994).

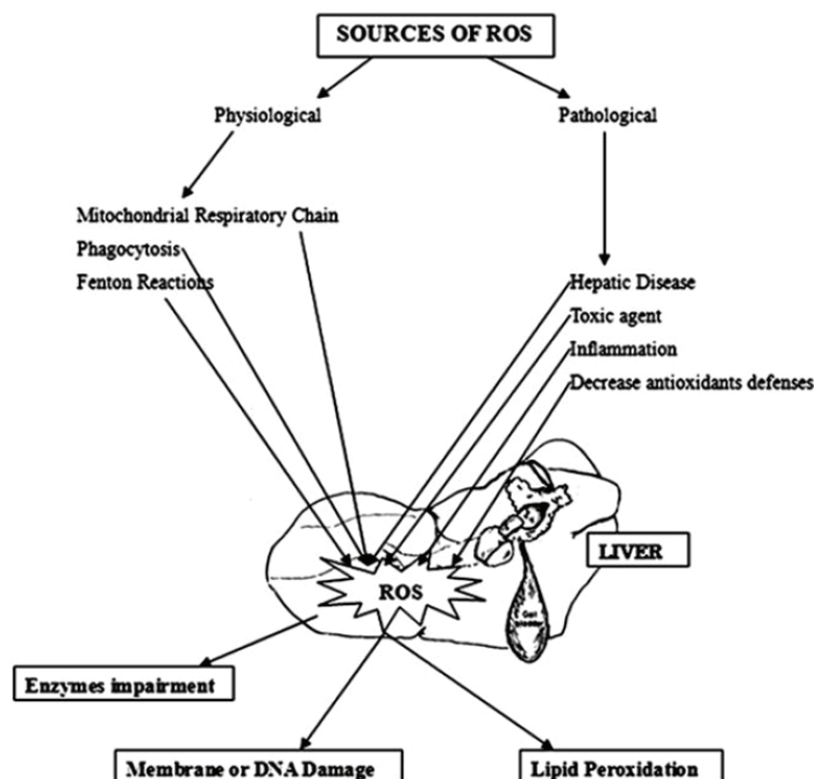Sources of ROS in the liver are summarized in Fig. 1.

Fig. 1. Sources of reactive oxygen species（ROS) in the liver (Abd Ellah et al., 2007)

3. Antioxidants and free radicals

The cells contain a variety of antioxidant mechanisms that play a central role in the protection against reactive oxygen species (Pár & Jávor, 1984; Halliwell, 1991). The antioxidant system consists of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px)), glutathione, ancillary enzymes (glutathione reductase (GR), glutathione S-transferase, and glucose 6-phosphate dehydrogenase (G6PD)), metal-binding proteins (transferrin, ceruloplasmin and albumin), vitamins (α-tocopherol, ascorbate and beta-carotene), flavonoids, and urate (Halliwell, 1994).

Pathological free radical reactions do not necessarily cause cell and tissue damage, as antioxidants of cells and tissues are able to prevent free radical injury (Feher et al., 1992). On the intracellular level, ROS formation and metabolism can be summarized as shown in Fig 2.

4. Hepatic oxidative stress and lipid peroxidation

Oxidative stress results when reactive forms of oxygen are produced faster than they can be safely neutralized by antioxidant mechanisms (Sies, 1991) and/or from a decrease in antioxidant defense, which may lead to damage of biological macromolecules and disruption of normal metabolism and physiology (Trevisan et al., 2001). This condition can contribute and/or lead to the onset of health disorders (Miller et al., 1993), and play a damaging role in a number of liver disorders, for example, in anoxic and reoxygenation injury during transplantation, activated phagocytes and xanthine oxidase formed during ischemia, catalyze the formation of superoxide during reperfusion (Southorn & Powis, 1988; Nauta et al., 1990; Brass et al., 1991; Rosser & Gores, 1995).
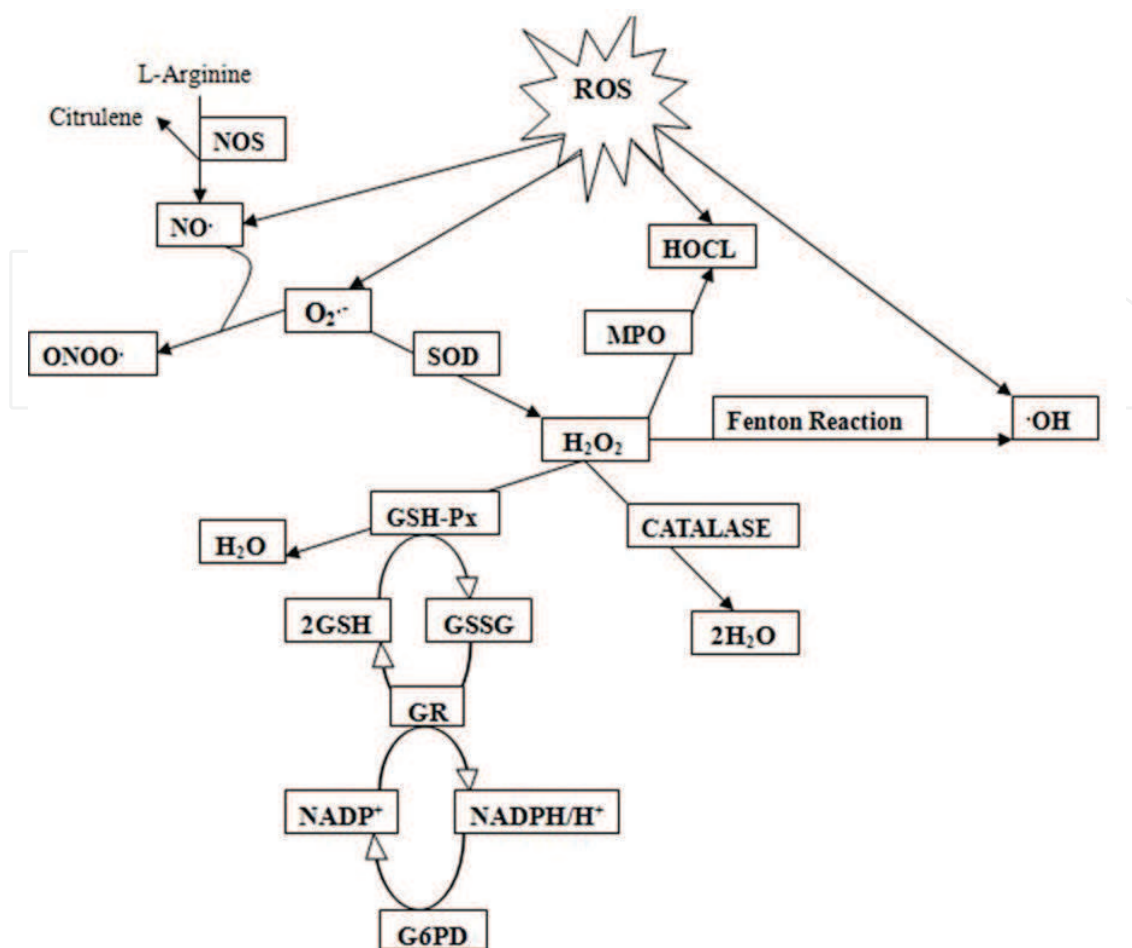
Fig. 2. Shows different types of reactive oxygen species (ROS). Abbreviations: Glutathione peroxidase (GSH-Px), Hypochlorous acid (HOCl), Hydrogen peroxide (H_2O_2), Myeloperoxidase (MPO), Nitric oxide (NO.), NO synthase (NOS), Superoxide anion ($O_2\cdot^-$), Hydroxyl radical ($\cdot$OH), Peroxynitrite anion (ONOO$\cdot$), Superoxide dismutase (SOD), Nicotinamide adenine diphosphate (NADPH), Reduced glutathione (GSH), Glutathione reductase (GR), Glucose-6-phosphate dehydrogenase (G6PD).

Lipid peroxidation is implicated in the pathogenesis of several hepatic disorders in human (Poli, 1993; Farinati et al., 1995) and animals (Mudroň et al., 1999; Abd Ellah et al., 2004). Hepatic failure in cattle was associated with decreased antioxidant mechanisms inside the cells, which led to the increase in the reactive oxygen species, especially H_2O_2. The decrease in hepatic GSH-Px activity in severe fatty degeneration, for example, results in the increase H_2O_2 (Abd Ellah et al., 2004), which can initiate free radical formation through Fenton's reaction. In addition, the decrease in hepatic vitamin E level, which is an important chain-breaking antioxidant, results in lipid peroxidation and failure to regenerate the ascorbic acid (Mudroň et al., 1997, 1999). Increased hepatic oxidative stress was also reported in cows suffering from glycogen degeneration (Abd Ellah et al., 2004), sawdust liver and liver abscesses (Spolarics, 1999; Abd Ellah et al., 2002; Sayed et al., 2003). The authors contended that the antioxidant defense was high in the case of sawdust liver, glycogen degeneration, and liver abscess, which indicated that the body can combat the increased free radical stress. Liver abscesses in fattening steers occur mainly due to intensive feeding of highly concentrated rations. Consumption of a carbohydrate-rich diet stimulates G6PD expression

in endothelial and parenchymal cells (Khan et al., 1987; Spolarics, 1999). Since G6PD supports reactive oxygen metabolism, the response may represent an antioxidant pathway in the hepatic cell populations that targets sinusoid born reactive oxygen species during infections (Spolarics, 1999; Abd Ellah et al., 2002).

Underfeeding in cattle was reported to induce changes in the antioxidant systems in liver manifested by lowering hepatic G6PD and SOD activities. This result in depletion of antioxidant defense mechanisms and render the hepatocytes more susceptible to the lethal effects of endogenous or exogenous peroxides, and indicate that the generation of lipid peroxides in cattle in poor nutritional condition exceeds the antioxidant capacity of the liver cells, generating a situation of oxidative stress and peroxidation (Sansinanea et al., 2000).

The leading mechanism of free radical toxicity is the peroxidation of membrane phospholipids, which is initiated by the formation of lipid peroxide or hydroperoxides, peroxy radicals are formed in the presence of oxygen to start a chain reaction (propagation) (Arthur et al., 1985; Poli, 1993; Bianchi et al., 1997). Various pathogenic effects occur as the result of degradation of membrane lipids (Stohs, 1995). Chiefly, the hydroxyl radical and to a lesser extent the superoxide anion leads to peroxidation of membrane lipids thereby causing production of malondialdehyde (MDA) and 4-hydroxyalkenals (4HNE). These substances directly induce hepatocytes damage with generation of proinflammatory cytokines, activation of spindle cells, and fibrogenesis (Pessayre et al., 2001; Younossi et al., 2002) and may bind to various molecules, impairing their functions (Zern et al., 1990) and therefore lead to membrane damage, protein damage, enzyme dysfunction and DNA or RNA damage (Vajdovich, 2001). It is well known that persistent oxidant stress causes mutative effects on cell DNA and increases fibroblastic activity, leading to cirrhosis and carcinoma. Many studies have shown that oxidative stress takes part in the pathogenesis of cholestasis by way of cytokines (Gonzalez-Correa et al., 1997, Wallace & Miller, 2000; Spirli et al., 2001; Alpini et al., 2002) and lipid peroxidation (Tsai et al., 1993).

The role for lipid peroxidation in liver fibrosis was assessed. Lipid peroxidation products in the form of MDA adduct were detected in areas of active fibrogenesis. It has been shown that lipid peroxidation products can stimulate fibrogenesis by inducing collagen gene expression, detection and prevention of lipid peroxidation could be of major interest in preventing fibrosis and cirrhosis in this disease (Paradis et al., 1997).

Increased lipid peroxidation may be caused by inflammation related to viral infection and decreased antioxidant levels. The lipid peroxides formed may be chemotactic for the neutrophils causing increased inflammation, which further drives oxidant-mediated injury in the liver (Deutsch, 1983). Previous studies have demonstrated an increase MDA levels and decreases the antioxidant capacity in acute and chronic hepatitis (Comporti, 1985; Poli et al., 1987; Bianchi et al., 1997). Mitochondrial lipid peroxidation takes place at varying levels in liver disorders independent of etiology (Sokol et al., 1994; Mansouri et al., 1997). Increased lipid, protein, and nucleic acid peroxidation in the blood and liver biopsy specimens from patients with chronic hepatitis has been demonstrated (Farinati et al., 1995; De Maria et al., 1996; Jabłonowska et al., 2005).

5. Oxidative stress and hepatic dysfunction: Role of liver biopsy

5.1 Blood and hepatic oxidative stress

Antioxidant status of blood doesn't reflect hepatic oxidative stress only, but their levels change in a response to diseases in other organs. Studying the effect of hepatic dysfunction

on blood oxidative status in cows revealed that hepatic glycogen degeneration, fatty degeneration or liver abscesses had no effect on erythrocytic oxidative status, as indicated by the insignificant changes in erythrocytes GSH-Px and G6PD activities (Abd Ellah et al., 2002, 2004). Many studies had been performed on humans to determine the effect of hepatic dysfunction on erythrocytic oxidative status, some of these studies had reported no significant changes in erythrocytes GSH-Px activity in patients suffered from liver cirrhosis and alcoholic liver disease (Johansson et al., 1986; Tanner et al., 1986; Akkus et al., 1997). Other studies had been demonstrated that a red cell GSH-Px activity significantly decreased in patients with chronic liver disease (Hadi Yasa et al., 1999; Chrobot et al., 2000; Czuczejko et al., 2003). In addition, lower activities of erythrocytes GSH-Px and SOD activities have been reported in patients with acute hepatitis B (Pak & Nikitin, 1991). The cause of such contradictory results may be related to the degree of hepatic dysfunction or the presence or absence of selenium deficiency. Significant decreases in plasma selenium level and erythrocytes GSH-Px had been reported in patients with chronic liver disease (Czuczejko et al., 2003).

Increased oxidative stress had been reported in the liver of cattle with naturally occurring fatty liver (Mudroň et al., 1999; Abd Ellah et al., 2004), with liver abscessation (Abd Ellah et al., 2002), and in animals on restricted feed intake (Sansinanea et al., 2000), without significant changes in blood oxidative status, this means that hepatic disease may present without effect on blood oxidative status, and also that detection of hepatic oxidative stress is best done through measuring oxidative stress markers in the hepatic tissues by means of liver biopsy.

5.2 Preparation of liver biopsy for antioxidants measurements

The principles for preparation of liver biopsy are: liver biopsy must be prepared directly after collection, otherwise stored at -80°C, liver biopsy must be washed twice in a cold saline or cold buffer before homogenization, blot dry and then homogenized in a cold buffer at certain pH. After centrifugation, the supernatant is harvested and used to measure hepatic antioxidant enzyme activities, which can be performed using commercial test kits (Table 1).

5.3 Liver biopsy and oxidative stress

Oxygen free radicals might play a role in the pathogenesis of tissue damage in many pathological conditions and has been implicated in a variety of liver diseases. It, therefore, may participate in the pathogenesis of toxic liver diseases and other hepatic alterations (Feher et al., 1998). Oxidative stress is a major pathogenetic event occurring in several liver disorders ranging from metabolic to proliferated ones, and is a main cause of liver damage in ischemia/ reperfusion during liver transplantation (Cesaratto et al., 2004).

The involvement of oxidative stress in the pathogenesis of liver injury has been investigated for many years (Comporti, 1985; Poli et al., 1987; Poli, 1993). Some of these studies were conducted using liver biopsy in human (Togashi et al., 1990; Ismail et al., 2010) and animals (Abd Ellah et al., 2008, 2009). But most of the studies in animals measured hepatic oxidative stress after slaughtering or euthanasia. Examples include, measuring hepatic G6PD activity in chemically induced hepatocellular carcinoma in rat liver (De Jong et al., 2001), and in liver of rat with macronodular cirrhosis induced by

long-term thioacetamide administration (Sanz et al., 1997). In cattle, hepatic GSH-Px activity (Abd Ellah et al., 2004) and vitamin E (Mudroň et al., 1997, 1999) were measured in cows suffered from severe fatty degeneration. In addition, hepatic GSH-Px and G6PD activities were determined in cows suffering from glycogen degeneration (Abd Ellah et al., 2004), sawdust liver and liver abscesses (Khan et al., 1987; Spolarics, 1999; Abd Ellah et al., 2002). Furthermore, hepatic G6PD and SOD activities were measured in cows with restricted feed intake (Sansinanea et al., 2000).

Tissue preparation	Buffer used	Homogenization	Oxidative stress marker	Reference
Liver biopsy samples were washed twice in cold 0.9% salt solution	Tris–HCL (50 mM) pH 7.5	The liver biopsy was homogenized in 20 volumes of cold buffer, and then the supernatant was harvested after centrifugation at 5000 g for 30 min at 4°C.	SOD, CAT and GSH	Abd Ellah et al. (2008, 2009)
	Chilled potassium chloride (1.17%)	Liver biopsy was homogenized in chilled buffer. The homogenates were centrifuged at 800 g for 5 min at 4oC to separate the nuclear debris. The obtained supernatant was re-centrifuged at 10,500 g for 20 min at 4°C to get the post mitochondrial supernatant.	SOD, CAT and MDA	Noori et al. (2009)
	Ice-cold PBS buffer (20 mM), pH 7.3 with 10 ml of 5mM butylated hydroxyl toluene	The tissue was homogenized in 290 ml ice-cold buffer. Following this, the suspension was centrifuged and supernatant was fractioned for analysis.	LPO and AOP	Madill et al. (2009)
	Tris-HCl (50 mM), pH 7.5, 5 mM EDTA, 1 nM dithiothreitol	The tissue was homogenized in 5 ml/g cold buffer. The homogenate was centrifuged at 10,000g for 15 minutes at 4°C. The supernatant was removed for assay.	GSH-Px	Ismail et al. (2010)
	Potassium phosphate (0.05 M) and 0.1 mM EDTA, pH 7.8	The tissue was homogenized in 200µL buffer and centrifuged at 15,000g for 30 minutes at 4°C. The supernatant was used for analysis.	SOD	Ismail et al. (2010)

Table 1. Methods for preparation of liver biopsy implemented in different studies

Recently, liver biopsy was applied as a tool for detecting hepatic oxidative stress in cattle from the viewpoint of the status of hepatic antioxidant enzymes after injection of a potent hepatotoxic (DL-ethionine), data were published (Abd Ellah et al., 2008, 2009). the supernatant of liver homogenate was used to measure hepatic SOD, catalase (Abd Ellah et al., 2009), total glutathione level and glutathione reductase activity (Abd Ellah et al., 2008).

Many studies were performed to establish the importance of liver biopsy from the viewpoint of oxidative stress in a variety of liver disorders in human. Examples in human include: Oxidative stress-related parameters were investigated in liver biopsy from NAFLD patients and used to assay activities of CAT and GSH-Px (Videla et al., 2004) Oxidative stress status in children with glycogen storage disease (Ismail et al., 2009)], and with cholestatic chronic liver disease (Ismail et al., 2010) was investigated by measuring GSH-Px, SOD and CAT activities in liver biopsy samples. Activities of SOD, CAT and GSH-Px were measured in liver biopsy specimens from patients with various liver diseases, including chronic persistent hepatitis, chronic active hepatitis, non-alcoholic cirrhosis, alcoholic cirrhosis and acute hepatitis (De Jong et al., 2001).

Increased hepatic oxidative stress had also been detected in liver biopsy from patients with cirrhosis and hepatocellular carcinoma, shown by the decrease of GSH-Px activity, hepatic and blood glutathione (GSH) levels, along with an increase the oxidized glutathione/glutathione ratio in cirrhotic (Farinati et al., 1995; Barbaro et al., 1999) and liver cancer tissues (Czeczot et al., 2006), which reflects both a decrease in the synthesize capacity of liver and the antioxidant defense.

It is clear from the above review of literature that liver biopsy can be used for measuring oxidative status of the liver tissues and that significant changes were detected in different hepatic dysfunction. Antioxidant activities in liver biopsy can be used to diagnose liver disease and as a prognostic factor for the liver disease under investigation.

6. Conclusion

Most of the studies done in animals were concerned with studying the hepatic oxidative stress after slaughtering or euthanasia. Studying the hepatic oxidative status in liver biopsy are lacking in animals. In human medicine, large number of studies was implemented to achieve this goal. Hepatic disease may present without significant effect on blood oxidative status, consequently. The best way is to measure hepatic oxidants and antioxidants in liver biopsy, which reflect the actual status of the liver.

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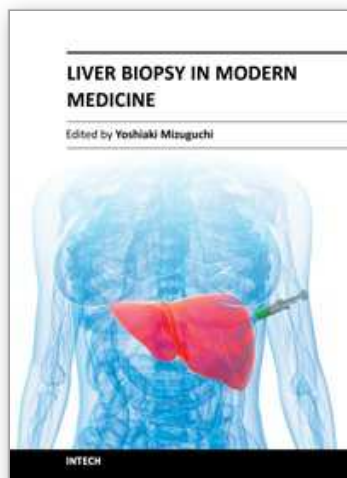
Liver Biopsy in Modern Medicine

Edited by Dr. Yoshiaki Mizuguchi

Liver biopsy, first performed by Paul Ehrlich in 1883, remains an important diagnostic procedure for the management of hepatobiliary disorders and the candidate/donated organ for transplantation. The book "Liver biopsy in Modern Medicine" comprises 21 chapters covering the various aspects of the biopsy procedure in detail and provides an up-to-date insightful coverage to the recent advances in the management of the various disorders with liver biospy. This book will keep up with cutting edge understanding of liver biopsy to many clinicians, physicians, scientists, pharmaceutics, engineers and other experts in a wide variety of different disciplines.

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