DOI:10.31557/APJCB.2021.6.4.316

REVIEW

A Study of the Relationship between Oxidative Stress and Risk of Developing Hepatocellular Carcinoma in People with Hepatitis B Infection; A Systematic Review Study

Hammadi Nour[1], Chouia Maroua[1], Derouiche Samir[1,2]

[1]Department of Cellular and Molecular Biology, Faculty of Natural Sciences and Life, University of El Oued, Algeria. [2]Laboratory of Biodiversity and Application of Biotechnology in the Agricultural Field, University of El Oued, Algeria.

Abstract

Introduction: Hepatitis B infection is a severe global public health issue. It is the 10th biggest cause of death worldwide. **Objective:** This review focuses on the relationship between oxidative stress and the risk of developing of acute and chronic hepatitis B complications. **Methods:** The data were collected by searching Science Direct, Google Scholar, PubMed, Scopus, Springer and National Center for Biotechnology Information (NCBI). The Keywords used as search terms were "Hepatitis B", "Acute and Chronic hepatitis", "HBV induced inflammatory reaction", "hepatitis B and Oxidative stress" and "free radical induced hepatitis B complication". **Results:** Chronic infections with chronic active hepatitis, acute or sub-acute hepatic necrosis, cirrhosis, liver failure, and hepatocellular cancer in people with hepatitis B infection are all complications of viral hepatitis. Extrahepatic complications are common in patients with chronic hepatitis infection, including cryoglobulinemia, non-Hodgkin lymphoma, focal lymphocytic sialadenitis, autoimmune thyroiditis, porphyria cutanea tarda, and lichen planus. Wide variations in hepatitis B incubation durations show that the redox state of cells can influence viral activity. Viral replication is more active with more severe oxidative stress, with dispersion from lysed or dead cells. Although the precise mechanisms of ROS participation in the pathogenesis of inflammatory disorders are still debated. **Conclusion:** Viral activity can be determined by the oxidative stress status of the cells which can be the main cause of the development of hepatocellular carcinoma related to the complications of acute and chronic hepatitis B.

Keywords: Hepatitis B- Oxidative stress- Hepatocellular carcinoma- inflammation

Asian Pac J Cancer Biol, **6 (4)**, 316-320

Submission Date: 12/23/2021 Acceptance Date: 12/30/2021

Introduction

Hepatitis B (HBV) infection is a severe global public health issue, with approximately 250 million people afflicted on a long-term basis [1]. It is the 10th biggest cause of death worldwide, accounting about 1.2 million fatalities per year. The prevalence of HBV infection varies significantly among geographic and demographic categories [2]. The area with the highest hepatitis B surface antigen (HBsAg) prevalence of >8% is Western sub-Saharan Africa, followed by Eastern sub-Saharan Africa, Central Asia, Southeast Asia, China and Oceania with a high intermediate prevalence of 5–7%; Latin America, Eastern Europe, North Africa, the Middle East, Turkey, Afghanistan, Pakistan, India and Australia with a low intermediate prevalence of 2–4% and the USA and Canada, Central America, Brazil and Western Europe with a low prevalence of <2% [3]. Different from HCV infection, the annual mortality rate from HBV infection in the USA did not change shown to be cost-saving in countries with high and intermediate endemicity [4]. Apart from exposure prophylaxis through personal protection measures, HBV vaccination should be administered to all unvaccinated individuals traveling to areas with high or intermediate HBsAg prevalence [5]. In viral hepatitis, cellular damage is predominantly determined by

Corresponding Author:
Dr. Derouiche Samir
Department of Cellular and Molecular Biology, Faculty of Natural Sciences and Life, University of El Oued, El-Oued 39000, Algeria. Laboratory of Biodiversity and Application of Biotechnology in the Agricultural Field, University of El Oued, El-Oued 39000, Algeria.
Email: dersamebio@gmail.com

the immune response and, although the pathophysiology is very complex, there are a very large number of data demonstrating that the persistence of infection, the progression of liver damage and carcinogenesis are all steps in which oxidative-mediated pathways are involved [6]. Many of recent landmarks in scientific research have shown that in human beings, oxidative stress has been implicated in the progression of major health problems by inactivating the metabolic enzymes and damaging important cellular components [7], it is as a consequence of increase a reactive oxygen species and decrease in antioxidant defenses in prevalent in many health problems [8]. Reactive oxygen and nitrogen species (ROS, RNS) play a crucial role in the induction and in the progression of liver disease, independently from its etiology [9]. They are involved in the transcription and activation of a large series of cytokines and growth factors that, in turn, can contribute to further production of ROS and RNS [10]. In light of these data, the aim of this review was to identify the role of oxidative stress as factors associated with acute and chronic hepatitis B development or complications.

Methods

The data were collected by searching Science Direct, Google Scholar, PubMed, Scopus, Springer and National Center for Biotechnology Information (NCBI). The Keywords used as search terms were "Hepatitis B", "Acute and Chronic hepatitis", "HBV induced inflammatory reaction", "hepatitis B and Oxidative stress" and "free radical induced hepatitis B complication"

Shapes of hepatitis B Particle

The hepatitis B virus is difficult to culture, but due to the large quantity of viral particles in sick people's serum, it was found early on using electron microscopy [11]. Infectious viral particles 40 to 48 nm in diameter, known as Dane particles, corresponding to complete virions, show three forms of structure. They have a core (nucleocapsid containing partly double-stranded DNA coupled with a DNA polymerase) and an envelope and are the least common [12]. Spherical particles or spherules with a diameter of 18 to 25 nm and filaments or tubules with a diameter of 22 nm and a length of 50 to 250 nm that could be aggregate spheres. These latter two pieces are similar to the envelope virus in structure and carry HBsAg [13]. They consist of an envelope consisting of a bilayer lipid and have a diameter of 25 to 27 nm. These non-infectious spherules and filaments are excess products [14].

Acute Infection

A moderate, asymptomatic, and subclinical sickness affects about two-thirds of individuals with acute HBV infection, which generally goes unnoticed [15]. A third of individuals with acute HBV infection have clinical hepatitis symptoms and signs, which can range from mild constitutional symptoms like fatigue and nausea to more severe symptoms like jaundice and, in rare cases, acute liver failure [16]. Acute hepatitis B has a clinical incubation time of 2–3 months, but it can vary from 1–6 months after exposure, with the length of the incubation period corresponding to some extent with the level of virus exposure [17]. A brief pre-icteric or prodromal period of constitutional symptoms such as fever, lethargy, anorexia, nausea, and body aches follows the incubation period. Serum ALT levels rise during this phase, and high levels of HBsAg and HBV DNA are detected. The pre-icteric phase can continue anywhere from a few days to a week and is followed by jaundice or dark urine [18]. The icteric phase of hepatitis B lasts 1–2 weeks and is characterized by a reduction in viral levels. Jaundice goes away after convalescence, although constitutional symptoms can remain for weeks or even months. HBsAg is eliminated, followed by the removal of detectable HBV DNA from serum, during this phase. Acute liver failure affects about 1% of people who have acute hepatitis B and jaundice [19]. Abdominal discomfort, fever, vomiting, and jaundice are common symptoms of fulminant hepatitis, which are often followed by disorientation, confusion, and coma [20]. HBV and HBsAg As liver failure progresses, DNA levels drop rapidly, and some patients are HBsAg-negative by the time hepatic coma sets in [21]. Acute liver failure caused by hepatitis B requires careful therapy and monitoring, and patients should be transferred to a tertiary medical hospital that offers liver transplantation as soon as possible [22].

Chronic Infection

The course of chronic hepatitis B is unpredictable and ever-changing. HBeAg, HBsAg, and HBV DNA are frequently present in high titers early in infection, and serum aminotransferase levels are mild to moderately elevated [23]. The severity of chronic hepatitis has a direct relationship with the patient's overall prognosis. The 5-year survival rate for people with severe chronic hepatitis and cirrhosis is around 50%. Many patients with chronic hepatitis (elevated ALT, inflammation, and/or fibrosis on liver biopsy) are asymptomatic or have vague symptoms including fatigue and mild right upper quadrant discomfort [24]. Acute exacerbations of chronic hepatitis with substantially increased serum ALT can occur in patients with chronic hepatitis. This scenario is more common in those with chronic hepatitis B who do not have HBeAg [25]. Anti-HBc IgM is a valuable marker for distinguishing between acute hepatitis B and chronic hepatitis B with a flare, as mentioned in the previous section. Anti-HBc of the IgM class, on the other hand, is occasionally found in patients with chronic hepatitis B who are experiencing an exacerbation [26]. Alpha-fetoprotein (AFP), which is regarded as a marker for HCC, is frequently raised in tandem with ALT during acute exacerbation. It is uncommon, however, to exceed 400 ng/mL [27]. The development of HCC should be suspected in patients with AFP levels significantly higher than this. An estimated one-third of people with chronic HBV infection may develop cirrhosis, end-stage liver disease, or HCC as a long-term consequence of the infection [28]. The determinants of outcome of chronic hepatitis B appear to be both viral (HBV DNA levels, HBV genotype, some HBV mutation patterns) and host-specific (age, gender, genetic background, immune status) [29].

Complications of Viral Hepatitis B

Chronic infections with chronic active hepatitis, acute or sub-acute hepatic necrosis, cirrhosis, liver failure, and hepatocellular cancer in people with hepatitis B or C infection are all complications of viral hepatitis [30]. Patients with hepatitis B are at a high risk of acquiring chronic infection and hepatocellular carcinoma, which accounts for 45 percent of primary liver cancer worldwide. About 1% of patients will suffer fulminant hepatic failure, with an 80 percent death rate [31]. About 75 to 85 percent of people with hepatitis C acquire chronic infection, and about 20% develop cirrhosis and eventually hepatocellular cancer [32]. Cirrhosis can lead to a variety of problems, such as hepatic encephalopathy, portal hypertension, ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatorenal syndrome [33]. Extrahepatic complications are common in patients with chronic hepatitis C infection, including cryoglobulinemia, which can cause a rash, vasculitis, and glomerulonephritis due to immune complex deposition in the small vessels, non-Hodgkin lymphoma, focal lymphocytic sialadenitis, autoimmune thyroiditis, porphyria cutanea tarda, and lichen planus [34].

Discussion

Oxidative stress refers to the imbalance between the production of reactive species and antioxidant defence. According to Sies oxidative stress is "a disturbance in the pro oxidant-antioxidant balances in favour of the former, leading to serious damage" [35]. Oxidative stress focuses the attention of worldwide researchers for its damaging effects on the human body [36] (Anand. 2014). and essential for life and also responsible for the death of a cell. In organisms including human's reactive oxygen species (ROS) and free radicals are produced during metabolic and immune system function [37]. Molecular oxygen (O_2) has ability to un-pair and leave free radicals which are unstable and highly reactive leads to formation of ROS [38]. Until the cellular redox equilibrium is disrupted, intracellular parasitic viruses may stay clinically dormant and without reactivation within host cells [39]. Wide variations in hepatitis B incubation durations show that the redox state of cells can influence viral activity. Viral replication is more active with more severe oxidative stress, with dispersion from lysed or dead cells [40]. Viruses use the host cell's synthetic processes to multiply, altering the endoplasmic reticulum and mitochondria's normal physiological biochemistry, resulting in increased ROS generation and antioxidant depletion [41]. Although the precise mechanisms of ROS participation in the pathogenesis of inflammatory disorders are still debated, ROS play a significant role in the pathogenesis of inflammatory diseases [42]. Parenchymal damage ranges from asymptomatic anicteric hepatitis to necroinflammatory hepatitis (acute, recurring, or chronic), cirrhosis, and cancer as a result of the resulting redox imbalance and oxidative stress (OS) [9]. The hepatitis B virus depletes antioxidants, and high levels of peroxidation products have a secondary effect on immunological cells. Chronic inflammation, iron excess, liver damage, and HCV-encoded proteins all contribute to systemic oxidative stress, which is most likely produced by a combination of chronic inflammation, iron overload, liver damage, and HCV-encoded proteins [43]. The increased generation of reactive oxygen and nitrogen species, together with the decreased antioxidant defense, promotes the development and progression of hepatic and extrahepatic complications of HCV infection [44]. Although HBV causes hepatitis, it appears to be particularly effective at causing oxidative stress, implying that the virus has its own oxidative stress-inducing mechanisms [45]. In sinusoids and areas of parenchymal necrosis, immunohistochemical examinations of biopsies from patients with acute hepatitis revealed the presence of vascular cell adhesion molecules ICAM-1, ELAM-1, and VCAM-1, as well as T-cell homing receptor [46]. This adds to our understanding of cytokine-induced upregulation of adhesiveness and recruitment of cytotoxic CD8 lymphocytes, followed by T-cell-mediated cell death via the release of cytotoxic substances like perforin and proteases (granzymes) or apoptosis via the FAS/Apo-1/CD 95 receptor system and mitochondrial dysfunction [47]. Apoptosis is induced by viral infection (in human liver diseases Councilman Bodies are the expression of apoptosis). This allows the virus to suppress or diminish the host immune response, allowing viral reproduction and spread [48]. TNF-, TGF-ß, IFN-ß, and IL-2 pathways influence apoptosis in HBV core, and these cytokines also alter the progression of liver injury to chronicity. The immune-mediated response of Th0/Th1 cytokines like IL-4 and IL-10, on the other hand, protects against the persistence of viruses and the formation of fibrosis [49].

In conclusion, Viral activity can be determined by the state of oxidative stress of cells, which can be the main cause of the development and complications of acute and chronic hepatitis B, and the most dangerous of them remains related to the emergence of complications related to liver cancer, and therefore it is necessary to take into account these phenomena in any approved treatment program, which may contribute to the prevention of Hepatitis B-related liver cancer and its complications.

Authors' contribution

CM participated in search and analysis of the paper. SD is the corresponding author. CM, HN and SD conducted the final edit and finalized the manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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