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Non-alcoholic fatty liver disease, to struggle with the strangle: Oxygen availability in fatty livers

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ABSTRACT

Nonalcoholic fatty liver diseases (NAFLD) is one of the most common chronic liver disease in Western countries. Oxygen is a central component of the cellular microenvironment, which participate in the regulation of cell survival, differentiation, functions and energy metabolism. Accordingly, sufficient oxygen supply is an important factor for tissue durability, mainly in highly metabolic tissues, such as the liver. Accumulating evidence from the past few decades provides strong support for the existence of interruptions in oxygen availability in fatty livers. This outcome may be the consequence of both, impaired systemic microcirculation and cellular membrane modifications which occur under steatotic conditions. This review summarizes current knowledge regarding the main factors which can affect oxygen supply in fatty liver.

1. Introduction

Aerobic organisms cannot survive without oxygen [1]. Oxygen is an important component of the cellular microenvironment, which regulates cell survival, differentiation and function. The liver is highly metabolic tissue, where oxygen is essential as an electron acceptor in energy metabolism. As such, adequate oxygen supply to the liver is extremely critical for this tissue's function [2,3]. Due to the liver structure and metabolism, the blood composition significantly alters during the passage through the sinusoids, leading to the formation of periportal-to-perivenous concentration gradients of substrates, products and hormones [3]. Oxygen partial pressure in the periportal blood (zone 1) is about 60–65 mm Hg (84–91 μmol/L, 9–11% oxygen) and falls as blood percolates throw the liver lobules towards the perivenuous (zone 3), where the oxygen partial pressure is about 30–35 mm Hg (42–49 μmol/L, 5–7% oxygen) [3,4]. Oxygen regulates metabolic zonation in normal liver and under pathological condition serves as a modulator of liver diseases [3]. Oxygen delivery also plays an important role in other hepatic process, such as hepatic redox state. It was also observed that reduced intrahepatic oxygen levels in zone 3 are associated with enhanced susceptibility of these cells to anoxia-induced damage [4]. These findings indicate that hepatocytes oxygen availability prior to the occurrence of stress can dramatically affect the outcome.

Non alcoholic liver diseases (NAFLD) encompass a wide spectrum of liver pathologies, ranging from simple steatosis through steatohepatitis (NASH) to cirrhosis. NAFLD is currently considered the most common chronic liver disease in Western countries and is steadily increasing along with the worldwide epidemic of obesity and type 2 diabetes (T2D) [5]. Substantial line of evidence suggests hepatic perfusion abnormalities exist in the presence of NAFLD. Moreover, it was further suggested that steatosis-induced reduced oxygen delivery to the liver may play a critical role in liver diseases related to steatosis [6]. In the present article we review several of the main causes for impaired liver oxygen availability under NAFLD. The consequences of such impairment are beyond the scope of this mini review.

2. Hepatic vascular network

The hepatic vascular network consists of dual distinct blood inflow systems: the hepatic artery, which delivers oxygen-rich blood and the portal vein which drains the gastrointestinal tract and delivers nutrient-rich blood [7]. The hepatic artery, contributes ~ 30% of the total hepatic blood flow and the portal vein, contributes ~ 70% of the total hepatic blood flow [8]. The intrahepatic branches of the portal vein, hepatic artery, along with the bile duct run together within the portal

Abbreviations: ALA, α-lipoic acid; AMPK, AMP-activated protein kinase; eNOS, endothelial NO synthase; ECM, extracellular matrix; ET-1, endothelin-1; **EVs**, **extracellular vesicles**; HCS, Hepatic stellate cells; HI, intermittent hypoxia; NO, nitric oxide; NAFLD, nonalcoholic liver diseases; NASH, nonalcoholic steatohepatitis; OSA, obstructive sleep apnea; PC, phosphatidylcholine; PE, phosphatidylethanolamine; RBS, red blood cells; ROS, reactive oxygen species; TXA2, thromboxane A2; T2D, type 2 diabetes

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tract system, branching out through ~ 17–20 orders of branches in order to deliver the entire corpus of the liver [9]. Finally, blood returned to the systemic circulation through at least three distinct hepatic veins (right, middle and left) which drains into the inferior vena cava.

The hepatic sinusoids comprise one of the largest-caliber vascular beds in the body [9]. Hepatic sinusoids are the location of pressure equalization between systemic and portal venous flow [10]. Impairment of blood flow through this vascular bed constitutes a major loss of physiologic function, with profound influence on homeostasis for the entire human organism [9].

Substantial changes in blood flow were demonstrated in human and animal models of fatty liver [11–15]. Recently, it was suggested that NAFLD may serve as a risk factor for the development of cardiovascular diseases primarily due to dysfunction in endothelial dependent vasodilation [16,17]. In relation to the hepatic vascular network, decreased portal vein flow was found in patients with fatty liver [18,19]. By using Doppler flowmetry, Seifalian et al. observed reduced sinusoidal perfusion in steatotic human liver grafts compared to healthy livers [11]. Decreased parenchymal perfusion was also found by using positron emission tomography in individuals with T2D and liver steatosis [20]. Likewise, Guiu and colleagues also found decreased perfusion-related diffusion in patients with T2D and liver steatosis, which was attributed to decreased parenchymal perfusion [19]. In accordance with human studies, several animal models of liver steatosis (rats, mice and rabbits) also demonstrate the presence of microvascular abnormalities in models of fatty liver characterized by the presence of reduced sinusoidal perfusion and dysfunctional sinusoids [11,12,15,21–24].

3. Morphology changes

Abnormal microvascular function and reduced oxygen consumption under steatotic condition can be explained by several mechanisms/factors. Previous studies have suggested that reduction in sinusoidal perfusion arises initially from the influence of enlarged hepatocytes. Increased accumulation of lipids within the cytosol causes the hepatocytes to swell (enlargement of cell size). Subsequently, this enlargement widens the paranchymal cell plates, narrow and distorts the lumens sinusoids and reduces the intrasinusoidal volume as well as the architecture of the sinusoidal network, leading to reduced oxygen supply to hepatocytes. Morphological changes of reduced sinusoidal perfusion area as a result of enlarge hepatocytes were corroborate by using microscopic methods in genetic animal models obese zucker rats (fa/fa), ob/ob and foz/foz mice and dietry-induced liver steatosis [11,25].

Importantly, reduction in oxygen availability can impair fatty acid oxidation, leading to further fat accumulation and exacerbation of fat-induced disturbances in sinusoidal perfusion, which generates a vicious circle of disease progression [25].

Extracellular vesicles (EVs) are lipid coated particles with a diameter of up to 1000 nm, which are released from different cell types. EVs and have been shown to have pathophysiological roles in a many disease states. NAFLD is consider the hepatic manifestation of metabolic syndrome. During a metabolic diseases organ crosstalk and lipid delivery from the adipose tissue to the liver or from liver non-parenchymal cells to hepatocytes could be a major factor for liver hypoxic/steatotic response. Indeed Evs released from adipose tissue may modulate liver steatosis [26]. A cross talk relationship was recently demonstrated between hypoxia inducible factor activation, nitric oxide production and EVs modulation. This has major response in endothelial cells EVs production [27], and could be an early marker for NAFLD [28].

4. Nitric oxide (NO)

NO is an essential vasodilator molecule. Beside this effect, intensive evidence further illustrate that NO involves in various processes that are beneficial to vascular homeostasis, including reduction of vascular smooth muscle migration and growth, platelet aggregation and thrombosis, monocyte and macrophage adhesion and inflammation [29].

Deficiency in endothelial NO synthase (eNOS)-derived NO may be important in the etiology of NAFLD. Alterations in NO metabolism and bioavailability can contribute to tissue injury under NAFLD as well as other NAFLD-related diseases, such as obesity and diabetes [30]. Decreased NO bioavailability was found in steatotic livers following high fat diet (HFD) or high cholesterol diet (diets induced steatosis) in rodents [24,30]. Impaired NO metabolism was associated with significant lower portal blood flow and reduced hepatic microcirculation. Conversely, in steatotic livers, L-Arginine administration improved hepatic arterial and portal blood flows as well as microcirculation and increased hepatic tissue oxyhemoglobin, whereas L-NAME significantly worsened these parameters [24]. Decreased NO bioavailability in diet-induced steatosis models was couples with changes in two key enzymes involved in the control of NO metabolism in liver, eNOS and/or arginase 1. Although total eNOS levels were not found to be profoundly altered, the extent of Ser1177 phosphorylation of eNOS was significantly decreased by a diet-induced liver steatosis [24,30].

Insulin is one of the main factors possibly involved in microvascular abnormalities and specifically in impaired eNOS activation observed in NAFLD. Beneficial vascular effects of insulin, particularly on the endothelium was demonstrated. Insulin promotes NO production through the activation of the PI3K/Akt/eNOS signaling pathway, leading to vasodilation and vascular protection [31]. NAFLD is often associated with insulin resistance [25]. Therefore, the development of insulin resistance under diet-induced liver steatosis might subsequently impairs insulin-induced vasodilation and cause the development of endothelial dysfunction, which further contribute to vascular damage [31]. Pasarin and colleagues [23] have demonstrated that vascular responses to insulin are indeed impaired in a model of early NAFLD and are associated with insulin resistance in the liver sinusoidal endothelium. By using a model of diet-induced obesity as well as isolated and perfused livers, they observed an increased hepatic vascular resistance with impaired vasodilatory response of the liver vascular bed to acetyl-choline. These abnormalities were associated with a decreased Akt-dependent eNOS phosphorylation and NOS activity which may impair endothelial dependent vasodilation. Importantly, in their studies, liver endothelial dysfunction occurred before the development of fibrosis or inflammation [23].

AMP-activated protein kinase (AMPK) has also been shown to phosphorylate and activate eNOS at Ser1177 in cultured endothelial cells [32]. It was suggested that treatments which induce liver/hepatic fat accumulation are also associated with abnormalities in AMPK activation [33–37]. However, the direct association between AMPK and eNOS phosphorylation and its effects on the microvascular system and endothelial function has yet to be shown. Nevertheless, Lee et al., have also demonstrated endothelial dysfunction in obese rats was associated with lower AMPK activating in aortic endothelium [38]. In their study, reduced AMPK activation was connected with impaired endothelium-dependent vascular relaxation and decreased NO synthesis. Administration of α-lipoic acid (ALA) normalized AMPK activation and improved endothelial function. However, eNOS phosphorylation was not assessed in that study. The postulated mechanism underlying reduced NO bioavailability was inactivation of NO by oxygen-derived free radicals. It was proposed that reduced AMPK activity leads to a decrease in fatty acid oxidation and an increase in intracellular malonyl coenzyme A levels. Thus, increased flux of free fatty acids (FFA) from the circulation concomitantly with decreased FFA oxidation in aortic endothelial cells would eventually lead to excessive accumulation of triglyceride and long chain acyl coenzyme A. This was suggested to be an initial event which leads to a cascade of increased reactive oxygen species (ROS) production, increased apoptosis, and decreased NO bioavailability in endothelial cells and vascular dysfunction.

Arginase 1 levels were found to be significantly increased by HFD