Leptin in NAFLD

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NAFLD is a worldwide health problem due to its increasing prevalence, so the research on its diagnosis, follow-up, and subsequent treatment has become essential. Moreover, NAFLD requires a multidisciplinary approach given its high risk of cardiovascular morbidity and mortality.

Keywords: fatty liver ; steatohepatitis ; obesity ; metabolic syndrome ; leptin

1. Introduction

Leptin is a 16 kDa adipocyte-derived hormone described for the first time by Zhang et al. (1994) as the product of theobese (Ob) gene[1], although its existence was predicted some decades before in leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice [2][3]. Leptin primary amino acidsequencesshow differences in vertebrates, while secondary and tertiary structures are similar [4] and alike to the long-chain helical cytokine family, which includes interleukin (IL) 6, IL-11 (interleukin 11), G-CSF (granulocyte-colony stimulating factor) or oncostatin M, among many others [5].

Leptin is characterized by having pleiotropic effects due to the great variety of leptin receptors (known as Ob-R or LEPR), thus being able to affect many biological processes at different levels. The six existing spliced Ob-R forms are called Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, Ob-Re and Ob-Rf, and belong to the class I cytokine superfamily [6][7] but differ from each other in the lengths of their cytoplasmic regions [8]. The most important leptin receptor is the long isoform Ob-Rb since it can fully transduce activation signals into the cell [9], including signaling pathways such as Janus kinase (JAK) 2/signal transducer and activator of transcription (STAT) 3, insulin receptor substrate (IRS)/phosphatidylinositol-3 kinase (PI3K), or Src homology 2 domain-containing phosphatase 2 (SHP2)/mitogen-activated protein kinase (MAPK) [10].

2. Leptin in the NAFLD Spectrum

NAFLD comprises a set of liver diseases, some of them irreversible. NAFLD development is divided into three main steps: simple steatosis, NASH, and liver cirrhosis. Simple steatosis is caused by factors such as high-fat and/or high sugar diet, obesity, T2DM, and other metabolic diseases, while NASH can be developed by inflammation and hepatocyte apoptosis. If liver fibrosis is provoked in this step, cirrhosis (and possibly HCC) will be also developed [11].

Hepatic steatosis has different degrees of severity related to liver damage in NAFLD: from simple steatosis to NASH, which is the most important disease in the NAFLD spectrum, since its prevalence is estimated to be approximately 1.5–6.5% in the general population, and considerably increasing this percentage in obese individuals [12]. Although most patients present isolated steatosis, about one third develop NASH, which confers a higher risk of progression to more advanced stages of NAFLD. In this step, inflammation develops when triglycerides levels exceed hepatic physiological adaptive mechanisms that leads to the process of lipotoxicity by which reactive oxygen species (ROS), endoplasmic reticulum stress and hepatocellular injury are produced. In turn, liver cell injury activates the immune and apoptotic pathways, leading to cell death.

One of leptin functions is to limit the storage of triglycerides in adipocytes and non-adipose tissues including the liver, thereby preventing lipotoxicity. Under normoleptinemia conditions, leptin exerts an anti-steatotic effect and improves insulin sensitivity by suppressing hepatic glucose production and lipogenesis [13][14]. Similarly, the anti-steatosis action of leptin has been observed in non-obese mice with uncontrolled type 1 diabetes mellitus (T1DM), in which such treatment induces a significant reduction of lipogenic and cholesterogenic transcription factors and decreases the lipids located in plasma and different tissues [15]. In this regard, one anti-steatotic mechanism carried out by leptin is to regulate components of the lipid synthesis in the liver, such as the transcription factor carbohydrate responsive element binding protein (ChREBP)

Leptin has also been suggested to have a synergistic effect when used together with insulin, probably inhibiting the production of very low-density lipoproteins (VLDL) [10][15][16]. According to this, leptin has been shown to improve insulin resistance and hepatic steatosis in lypodystrophic mice [17]. (2019) showed that brain leptin protects from ectopic lipid accumulation and could be a therapeutic strategy to improve obesity-related steatosis [18]. Moreover, this disease has been shown to alleviate upregulating leptin levels by using metformin [19] and through leptin signaling pathways by using a modification of Samjunghwan, an herbal formula used in traditional Korean medicine [20].

By contrast, high leptin levels have also been associated with hepatic steatosis and NAFLD pathogenesis since a high percentage of NAFLD patients have been observed to suffer obesity, which is closely related with hyperleptinemia [21][13] [22]. The failure of elevated leptin levels to correct hepatic steatosis lies in the generation of a state of resistance to this hormone. The severity of hepatic steatosis correlates with leptin levels, especially in patients with high BMI. (2011) showed that steatosis grade at baseline was significantly greater as leptin concentrations increased in chronic hepatitis C patients [23] and Eshraghian et al.

In NAFLD, most patients have simple steatosis, but those with NASH can advance to the next step of the disease, which is fibrosis. The mechanisms of progression from simple steatosis to NASH are not entirely clear, but some factors are known to be involved in the process [24], including an inflammation caused by the incomplete oxidation of hepatic accumulated lipids, which generates toxic metabolites and produces apoptosis of hepatocytes, thus activating inflammatory cells [25]. If inflammation becomes chronic, then fibrosis will be developed [26]. Related to this, leptin could promote NAFLD by playing its well-known role in the inflammatory process [27].

Advanced fibrosis implies an increased risk for developing other NAFLD-related complications, such as cirrhosis and HCC. For that reason, an early diagnosis of patients with advanced fibrosis is crucial [28]. (2018) showed that leptin levels were simultaneously increased with the degree of liver fibrosis, especially in patients with a high BMI, while their lean counterparts had lower rates of fibrosis and inflammation [29]. Some studies have reported that Ob-R on Kupffer cells (KC) and sinusoidal endothelial cells increases the expression of matrix remodeling enzymes, which induce the fibrosis cascade in hepatic stellate cells (HSC).

Activated HSC also contribute to increase inflammation and liver fibrosis by releasing TGF-β1, angiopoietin-1, VEGF (vascular endothelial growth factor), and collagen-I. In addition, HSC appear to produce leptin, and have also been proposed to express Ob-Rb, which establishes a vicious cycle by stimulating proliferation and preventing apoptosis of HSC and thus affecting hepatic inflammation and fibrosis [30]. KC can be activated by leptin via peroxynitrite-mediated oxidative stress [31], which promotes CD8+CD57+T cells, found in NASH progression [32]. Also, prolonged hyperleptinemia may result in HSC, KC, and sinusoidal cell activation, that could trigger both the proinflammatory and profibrogenic cascade [13].

According to several studies with small sample sizes, progression from NASH to liver cirrhosis can occur in up to 25% of patients. This high disease burden has led to an increase in the number of NASH-related transplants, possibly becoming in the leading cause of liver transplantation worldwide in coming decades, displacing the hepatitis C virus [33]. Up to now, leptin concentration in patients with NAFLD-related cirrhosis has not been studied. However, leptin is known to induce VEGF on HSC, contributing to the irreversibility of cirrhosis and, potentially, to NASH progression [34].

There are references in other types of liver cirrhosis about leptin, in which this hormone has been demonstrated to be in both high [35] and low [36] levels. Even leptin has also been found to be uncorrelated with the existence of cirrhosis in alcoholic liver disease [37]. Interestingly, Ockenga et al. (2007) analyzed in vivo hepatic substrate and leptin metabolism in 40 patients with liver cirrhosis and 31 healthy controls, showing that patients had bound leptin and soluble leptin receptor levels significantly increased when compared with controls, without changes in free leptin, suggesting a different role for those components in both metabolic and inflammatory processes in cirrhotic patients [38].

Obesity and T2DM are cancer promoters and, in coexistence with NAFLD, the aggressive potential can be underestimated. In this regard, HCC incidence increased by 3% per year in the last decade, unlike other malignancies also associated with obesity, such as breast or colon cancer, whose incidences remained stable or decreased. The mechanisms of HCC development in a cirrhotic liver include destruction of hepatocytes due to chronic injury, and their subsequent regeneration and compensatory cyclic proliferation. NAFLD patients usually present insulin resistance which, together with hepatic steatosis and chronic low-grade inflammation, favors the creation of an ideal environment for tumor development and growth [39].

In fact, in vitro studies suggest that this hormone is increased during the proliferation, migration, and invasiveness of HCC cells through activation of PI3K/AKT signaling pathways, mainly in obese patients [40] and have been demonstrated to take part in the angiogenesis process [41], as well as both JAK2/STAT and ERK pathways [42]. In line with this, a lack of

leptin action has been shown to reduce the angiogenic process in experimental steatohepatitis [43]. Moreover, the analysis of circulating leptin levels has been found to be increased in both cirrhotic and non-cirrhotic patients regardless of the previous pathology [44], including NASH [45]. In this regard, more studies have also reported the role of leptin and Ob-R as a critical regulator in HCC development and progression [41][46][47].

However, Elinav et al. (2006) suggested a beneficial role of leptin in HCC murine models since this hormone decreased tumor size and improved survival [48]. In the same year, similar conclusions were drawn by analyzing both leptin and Ob-Rb in HCC patients [49][50]. Despite this, there is sufficient evidence to suggest the critical role of leptin in liver carcinogenesis, that may also be potentially fostered by NAFLD progression.

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