

Leptin and Non-Alcoholic Fatty Liver Disease: Hints From Preliminary Clinical Studies

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The product of the *ob* gene leptin was first identified and cloned from rodent adipose tissue in 1994. It was pioneerly considered to play a role in the regulation of the energy balance, as leptin deficient *ob/ob* mice showed typical features of metabolic syndrome (MS). Individuals that less responsive to the action of leptin led to the concept of leptin resistance. Multiple biological processes can promote leptin resistance and thus interfere with related diseases [1]. Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of MS became world epidemics along with other MS components such as diabetes, obesity, and leptin resistance is indicated in the process [2].

Leptin can regulate the development of NAFLD indirectly, centrally acting on multiple neurons through leptin receptors (LepR) in the brain and involve in anorexigenic peptide expression, or directly binding LepR in peripheral and implicated in a broad range of physiological processes [3]. Quite number of studies revealed the relationship between leptin and NAFLD, the anti-steatotic, anti-inflammatory and anti-fibrogenic roles of leptin in NAFLD models have been proved by experimental studies, whereas the data from clinical studies in NAFLD patients are not that consistent [4].

Animal studies confirmed that circulating leptin level are in proportional to body fat content, and NAFLD models usually showed higher levels of leptin in comparison to the controls. In view of clinical data derived from biopsy-proven NAFLD patients, some authors reported higher leptin levels, whereas others reported similar levels between NAFLD patients and healthy controls. However, there is no study showed lower leptin levels in NAFLD patients than controls up to now. Likewise, in some more severe steatosis, inflammation and fibrosis grade patients and progressive non-alcoholic steatohepatitis (NASH) patients, some but not all cases showed higher leptin levels than the controls or the mild stage patients [4].

Leptin acts through LepRs, which belong to the cytokine receptor class I family. Regarding LepR, lower circulating LepRb, the predominant subunit of LepR in NAFLD patients than controls were reported [5]. The soluble LepR (sLepR), which is considered as the carrier for leptin is also found to be decreased in NAFLD

patients [6]. In both studies, the circulating LepR levels were inversely correlated with leptin levels, indicating the possibility that any positive or adverse consequences of the increasing leptin. However, not all studies get the same conclusion, some other investigators reported no association of sLepR levels with NAFLD, while still others presented sLepR levels were positively correlated with the stage of hepatic fibrosis [7, 8]. These controversial results might be attributed to differences in populations (age, race, BMI, et al), inclusion criteria (staging and grading of the disease, co-morbidity et al). Another important issue is the complex in defining NASH, even if graded or staged with the same histological system, it might be not reflect the severity of disease, Furthermore, the levels of circulating leptin can be affected by BMI, while the change of BMI is not that consistent with the severity of NAFLD. Finally, leptin may act on the liver through autocrine or paracrine, therefore, the levels of circulating leptin may insufficiently reflect the diseases.

As for the leptin and leptin receptor gene expression evaluation in NAFLD populations, a small size study that based on immunohistochemistry technique has revealed higher hepatic leptin expression in NAFLD patients [9], while another two studies found no leptin gene expression in the liver [10, 11]. In a single nucleotide polymorphisms (SNPs) network analysis study, carriers of the G allele of patatin-like phospholipase domain-containing 3 (PNPLA3) SNP rs738409 showed lower peripheral LEP expression, together with higher rates of hepatic steatosis compared with CC genotype. Another SNP study showed GG homozygous showed

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73% higher hepatic fat content as compared with CC homozygous, and also the risk of progressive inflammatory and fibrosis is also significant increased [12]. Even these results are attracting, the data need to be carefully interpreted, since the studies are observational, no cause-effect mode can be established. On the other hand, large sample size studies are deficient in SNP studies because of the lack resource of getting liver tissues, the data attained may not achieve statistical power.

The aforementioned clinical data from cross-sectional studies need to be cautiously interpreted, and the results may need further verification. However, these preliminary studies indicate leptin is an active player in the development of NAFLD, and the change of leptin is differ in different stages of NAFLD, thus clarifying the mechanism of leptin in NAFLD may help to guide strategy making in phase treatment on NAFLD patients.

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