









A narrative review on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis versus hepatocellular carcinoma: do you mind?

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a predominant etiologic factor for liver disease. The risk of the development of hepatocellular carcinoma (HCC) in cases suffering from NAFLD has been stated¹. Nonalcoholic steatohepatitis (NASH), a subtype of NAFLD, is a well-known etiologic factor for cirrhosis and it is one of the risk factors for the development of HCC². In addition, the association of obesity with NAFLD is well established and augmentation in obesity has been associated with an increase in the incidence of HCC^{1,3}.

In the present review, the interrelation of NAFLD and HCC, obesity and NAFLD, and obesity and HCC has been purposed to be discussed by taking into consideration the relevant prevalence, clinical evidence, pathogenic mechanisms, and diagnostic parameters.

METHODS

We have performed searching the data from online databases such as PubMed/MEDLINE and Google Scholar by using the following key words: nonalcoholic fatty liver disease/NAFLD, hepatocellular carcinoma/HCC, obesity, and NASH. The data have been included in various studies and review articles.

An association of non-alcoholic fatty liver disease and hepatocellular carcinoma

Prevalence

A review of worldwide data indicates that NAFLD is a prevalent chronic disorder and different types of data reveal its prevalence ranging from 6% to 35%⁴. Some of the cases with NAFLD land up in the complication “HCC,” as the data from a meta-analysis by Younossi et al.¹ indicate that the incidence of HCC is 0.44 per 1,000 person-years. However, liver cirrhosis is a complication of NASH and it further leads to HCC. Ascha et al.² reported that HCC was found in 2.6% of cases suffering from NASH-associated cirrhosis¹. In addition, the increased death rate has been reported in cases suffering from NASH due to HCC, especially in NASH patients suffering from advanced fibrosis. Hashimoto et al.⁵ reported a survival rate of nearly 83% in 5 years in those suffering from HCC, especially in NASH cases suffering from advanced fibrosis⁵. The steatohepatitic hepatocellular carcinoma (SH-HCC) variant was noted in approximately 35% cases of HCC: a distinctive histological variant of HCC in hepatitis C virus related cirrhosis associated with NAFLD/NASH⁶.

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Clinical evidence

As per a retrospective cohort study conducted in a large number of patients by Kanwal et al.⁷, the prevalence of HCC was higher in patients, particularly in those who were suffering from NAFLD, and the incidence rate of HCC was significantly augmented in NAFLD patients with cirrhosis. In that study, nearly 297,000 NAFLD cases were compared with a similar number of controls. Nearly 500 patients with NAFLD developed HCC (0.21/1,000 person-years). In addition, an association of NAFLD or NASH and an increased risk of HCC was established in the systematic review by White et al.⁸, and the risk of HCC was particularly higher in cirrhotic NAFLD or NASH cases. Researchers reviewed a total of 57 studies (cohort studies, case-control, cross-sectional studies, and case series) to establish this association⁸. The results of a meta-analysis of a large cohort study, including approximately 19 million people with approximately 137,000 NAFLD/NASH patients, revealed higher risks of cirrhosis and HCC in the NAFLD/NASH cases and significantly increased risks of cirrhosis and HCC in the NASH cases with high-risk Fib-4 scores⁹. In addition, Bugianesi et al.¹⁰ reported a predominantly increased numerical value of the NASH in HCC cases with cryptogenic cirrhosis, by comparing the HCC cases with viral and alcohol-associated liver disorders.

Pathogenesis

The pathogenesis of HCC from NAFLD was elaborated by Takakura et al.¹¹, including the following steps and/or aspects:

- i. The progression of NASH to HCC was associated with an inflammatory pathway inclusive of tumor necrosis factor (TNF).
- ii. A diet containing a higher amount of fat leads to increased stress in the endoplasmic reticulum (ER).
- iii. Increased stress in the ER leads to increased lipogenesis or steatosis in the liver.
- iv. Increased stress in the ER and lipogenesis contributes to the increased synthesis of reactive oxygen species (ROS) that result in the rise in oxidative stress and contributes to genomic instability.
- v. Increased ER stress coupled with oxidative stress activates inflammatory mediators.
- vi. Macrophages release TNF that causes hepatocyte proliferation and expansion of HCC progenitors.
- vii. TNF further activates chemokines and growth factors/cytokines.
- viii. Dysbiosis leads to liver fibrosis and carcinogenesis through the involvement of the microbiota-liver axis.

- ix. Intestinal microbiota and pathogen-associated molecular patterns (PAMPs) are etiological factors for liver disorders through the route of the portal vein.
- x. Patients with NAFLD and NASH have raised intestinal permeability and excessive growth of intestinal bacteria.
- xi. The synthesis of TNF- α in Kupffer cells is stimulated by lipopolysaccharide (LPS) in portal blood through a rise in the Toll-like receptor 4 (TLR4) signal.
- xii. Increased sensitivity to transforming growth factor-beta (TGF- β) by LPS leads to the development of liver fibrosis and tumorigenesis in the liver.
- xiii. Increased levels of deoxycholic acid (DCA) contribute to the senescence of stellate cells which further causes hepatocarcinogenesis via the senescence-associated secretory phenotype (SASP) factor.
- xiv. Pathways of STAT-1-dependent NASH and STAT-3-dependent HCC from fatty liver.
- xv. Pro-tumorigenic signaling pathways are stimulated in HCC.
- xvi. Signal transducer and activator of transcription-3 (STAT-3) signaling leads to the transformation of tumor progenitors and progression to HCC.
- xvii. STAT-3 suppresses the activity of T cell protein tyrosine phosphatase (TCPTP) that leads to HCC in obesity.

In addition, older age and advanced fibrosis are predominant risk factors for HCC; therefore, ongoing screening for HCC is reported as being essential for NASH patients with advanced fibrosis⁵.

An association of obesity and non-alcoholic fatty liver disease

Prevalence

As per a meta-analysis of 86 studies from 22 countries, the prevalence of obesity among patients with NAFLD was projected at 51% by Younossi et al.¹. As per a review by Milić et al.¹², NAFLD is the most prevalent liver disease worldwide. NAFLD is demonstrated as either steatosis or NASH, and central abdominal obesity contributes to the causation processes of NAFLD; thus, it is reported that up to 80% of cases with NAFLD are obese¹².

Clinical evidence

Overweight and obesity, per se, are stated as a kind of legacy for the accrued prevalence of NAFLD in metabolically healthy

men and women as an outcome of a large cohort study conducted in nearly 77,000 men and women free of NAFLD and metabolic abnormalities at baseline. Nearly 10,000 participants developed NAFLD with a prevalence rate of approximately 30/1,000 person-years¹³. A study conducted by Bertola et al.¹⁴ reported upregulation of genes associated with inflammatory and immune response and that further leads to T-cell stimulation in morbidly obese patients by serum palmitate stimulation of the TLR pathway that contributes to the development of steatosis.

Pathogenesis

The pathogenesis of obesity and NAFLD was elaborated by Jennifer et al.¹⁵ as follows: Researchers have reported that obesity is a major or at least a contributing risk factor for NAFLD. The National Health and Nutrition Examination Survey III stated that nearly 7% of lean adults and approximately 28% of overweight/obese adults had hepatic steatosis, and the visceral adipose tissue (VAT) is predominantly associated with NAFLD. It is reported that VAT is significantly related to liver inflammation and fibrosis. The hormonal and biological activity of adipose tissue through secretion of adipokines by white adipocytes, the release of inflammatory cytokines by macrophages within adipose tissue, and the release of free fatty acids from adipocytes are increasingly recognized as contributing to insulin resistance (IR) and metabolic disease, including NASH. The following factors lead to IR, NAFLD, and NASH: i) the hormonal and biological actions of adipose tissue through secretion of adipokines by white adipocytes, ii) secretion of inflammatory cytokines by macrophages within adipose tissue, and iii) secretion of free fatty acids from adipocytes. As per a review of different data by Milić et al.¹², VAT leads to a rising incidence of NAFLD in morbidly obese cases. It has also been reported that secretion of adipokines from VAT as well as lipid accumulation in the liver further promote inflammation through nuclear factor kappa B signaling pathways that are stimulated by free fatty acids, leading to IR¹².

In obese individuals, stored fat in the abdomen has an impact on the metabolism of fat and glucose and stored fat-containing liver is insulin-resistant. IR is often associated with chronic inflammation, and numerous mediators released from immune cells and adipocytes are propounded as the causative factors for

IR. These mediators have also been expressed to contribute to the development of NAFLD¹⁶. We also currently emphasized possible metabolic, environmental, and genetic associations of NAFLD versus HCC¹⁷. Finally, NASH is also connected with cryptogenic cirrhosis particularly in the elderly patients with type 2 diabetes mellitus and obesity¹⁸.

CONCLUSIONS

Of note, a significantly increased number of HCC patients with cryptogenic liver disease had well-differentiated tumors than in HCC patients with chronic viral hepatitis and alcoholism. As such, HCC is one of the debilitating complications of NAFLD/NASH and obesity is a causative factor for NAFLD/NASH. Thus, various preclinical and clinical data suggest that obesity appears to be an important causative factor in the progression of NAFLD/NASH to HCC.

AUTHORS' CONTRIBUTIONS

DT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **IS:** Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **AP:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **DS:** Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **PV:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **PI:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **JR:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **CK:** Validation, Visualization, Writing – review & editing.

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