Review Article

Impact of chronic psychological stress on nonalcoholic fatty liver disease

Shuang Zhang1, Chongyang Ma1, Xueqian Wang1, Qingguo Wang1, Wenting Song2, Changxiang Li1, Changming Zhai3, Yuqing Qi1, Shuning Fan1, Fafeng Cheng1

1School of Basic Medical Sciences, Beijing University of Chinese Medicine, 11 Beisanhuandong Road, Chao Yang District, Beijing 100029, China; 2Xiyuan Hospital CACMS, Beijing 100091, China; 3Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing 100029, China

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases, worldwide, with increasing prevalence. NAFLD affects the lives of many people, greatly harming overall health. The present review discusses the potential roles of psychological stress in the pathogenesis of NAFLD, based on a growing number of clinical trials and animal experiments. Evidence from clinical and experimental studies has shown that psychological stress produces a marked impact on inflammation. The underlying mechanisms have a close correlation with metabolic disorders. Stress-induced alterations in the hypothalamic-pituitary-adrenal (HPA) axis may cause symptom exaggeration in NAFLD. NAFLD is a stress-sensitive disorder. Therefore, treatment of NAFLD should focus on management of stress and stress-induced responses. An integrative approach for NAFLD management is necessary.

Keywords: Chronic psychological stress, hypothalamic-pituitary-adrenal (HPA) axis, inflammation

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western countries, affecting 17-46% of adults. Incidence rates differ according to diagnostic methods, age, sex, and ethnicity [1]. In China, the prevalence of NAFLD among adults in the general population is approximately 15% (6.3-27.0%) [2]. NAFLD is characterized by excessive hepatic fat accumulation, closely associated with obesity, insulin resistance (IR) hypertension, and dyslipidemia. This suggests that NAFLD could be the liver’s manifestation of a metabolic syndrome [3, 4]. NAFLD includes two pathologically distinct conditions with different prognoses, including non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH). The latter covers a wide spectrum of severe diseases, including fibrosis, cirrhosis, and hepatocellular carcinoma [5]. Moreover, 5-10% of NAFLD develops into NASH. At present, the molecular mechanisms and pathological events underlying the progression of NAFLD to NASH remain incompletely understood, despite the high prevalence. No pharmacological agents for treatment of NAFLD exist [6]. However, most recently, evidence has suggested that the activation of selective molecular pathways plays a key role in development of excessive inflammatory responses.

In 1884, William James famously asked if one would run away from a wild bear out of fear or whether the fear would come from running away [7]. The following discussion on the interrelationships between physiological and psychological stress responses suggest the consistent association between physiological and psychological states during stress. Stress has been broadly defined as a process in which adverse environmental demands exceed the adaptive capacity of an organism [8, 9]. This results in psychological and physiological changes that may place persons at risk for disease [10, 11]. Although sensing and reaction to stress has evolved to promote adaptation to a new condition, modern work habits and lifestyles present challenges that could render individuals susceptible to physical and mental...
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Previous studies have shown clinical and preclinical evidence of the essential roles of chronic psychosocial stressors in the etiology and progression of obesity [15] and metabolic dysregulation [16]. Growing scientific evidence has demonstrated the detrimental effects of psychosocial stress on liver diseases in humans and animals [17]. Moreover, chronic psychological stress could lead to systematic inflammatory activity [18]. The current study gathered clinical and experimental evidence concerning the possible involvement of chronic psychological stress in the process of NAFLD, explaining this phenomenon by focusing on the roles of cross talk between inflammation and lipid homeostasis.

**Effects of chronic psychological stress on NAFLD**

**Evidence from clinical research**

Poor interpersonal relationships, work and unemployment pressure, low self-esteem, and low socioeconomic status often lead to chronic psychological stress. Previous studies have indicated that policing is one of the most stressful occupations. High work stress has been associated with metabolic syndrome (MetS) with police officers [19, 20]. Occupational stress was found to be a risk factor for NAFLD for Chinese police officers [21]. Psychological factors, such as depression and anxiety, which are closely related to psychological stress, are related to NAFLD severity, according to a systematic review of NAFLD/NASH [22, 23]. A previous study showed that the risk for severe hepatocellular balloon degeneration (NASH stage markers) in patients with depression and anxiety is 2.1 and 3.6 times, respectively, higher than that in other patients [23]. Some studies have also suggested that emotional problems could influence the progression of chronic liver diseases, including NAFLD/NASH. Elwing et al. compared patients diagnosed with non-alcoholic steatohepatitis (NASH), a more severe form of NAFLD, with matched controls without liver disease in terms of emotional disorders. Major depressive disorder and generalized anxiety disorder diagnoses were established based on the DSM-IV criteria prior to diagnosis of liver disease. The authors concluded that major depressive and generalized anxiety disorders are more frequent in patients with NASH and are associated with more advanced liver histological abnormalities [11]. Moreover, the purpose of the investigation was to develop a hypothesis regarding the relationship between psychosocial factors and weight. Fifty-eight participants with obesity that were overweight with NAFLD completed baseline measurements of personality, psychiatric symptoms, and readiness for behavioral change. They were followed up for 6 months with standard care. Depression, low conscientiousness, and high neuroticism were associated with higher weights at 6 months of follow-up, with small to large effect sizes [24]. NAFLD has been thought to be the liver’s pathological manifestation of metabolic syndrome (Metabolic syndrome, MetS). Puustinen et al. followed an average of 466 patients with MetS-free NAFLD for 6.4 years. They found a high degree of psychological distress at baseline in patients that developed MetS (odds ratio, OR = 2.18) [25]. However, the diagnosis of NASH requires liver biopsies and there are difficulties in conducting psychological stress-related diagnosis and follow-ups. Thus, conducting clinical research to determine whether chronic psychological stress could induce or aggravate NAFLD appears to be a huge undertaking.

**Evidence from animal studies**

To address the hypothesis that chronic stress is associated with NAFLD development, an experimental study subjected C57bl/6 mice to electric foot shock and restraint stress for 12 weeks, setting up a chronic stress model. In the stress group, the hepatic index was significantly elevated, despite the lower food intake and weight gain. Quantitative analysis of liver triglycerides (TG), total cholesterol (TC) concentrations, and oil red O staining showed that TG and TC levels in the stressed mice were significantly increased. Thus, chronic stress could induce hepatic steatosis, unrelated to diet [26]. Some researchers selected a chronically stressed rat model [27]. They found that chronic stress could result in high serum alanine transaminase (ALT) and aspartate transaminase (AST) levels, high liver interleukin-6 (IL-6) and malondialdehyde (MDA) levels, and low serum TG levels. Liver free fatty acid (FFA), TC, TG, and low-density lipoprotein levels significantly increased the levels of liver superoxide dismutase (SOD). Increased retention of hepatocyte lipids, in the form of TG and TC, is a
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common early feature of NAFLD. High levels of serum ALT and AST indicate the ability of chronic stress in hepatocellular injuries. IL-6 is a proinflammatory multifunctional cytokine produced by adipocytes, hepatocytes, and immune and endothelial cells [28]. Some studies have shown that accumulation of FFA in hepatocytes activates IκB kinase and NF-κB, which is a transcription factor playing an important role in coordinating the expression of various proinflammatory cytokines (including IL-6) [29]. Increased levels of MDA and reduced SOD activity are significant signs of increased oxidative stress [30, 31]. Thus, these results further confirm the pathogenesis of stress-related NAFLD.

Macedo et al. [32] found that the weight of mice fed with a high-calorie diet in the chronic stress model (narrow living environment) decreased, compared with that of those fed with a normal diet. However, the body weight/body length ratio was not significantly reduced, suggesting the possibility of abdominal obesity. Czech et al. [33] found that the liver, in a chronic stress mice model fed with normal diet, showed significant oxidative stress and inflammatory response, relative to the living environment of mice. Although stress models used in previous studies were different, they suggested that stress is associated with hepatic steatosis and inflammatory response.

Mechanisms of the effects of chronic psychological stress on NAFLD [Figure 1]

Chronic stress affects neurogenic and neurotrophic pathways that maintain ionic homeostasis [34]. Bo Jiang et al. found that some biochemical agent (SKF83959)-induced neurogenic and neurotrophic effects are mediated by the brain-derived neurotrophic factor (BDNF) system [35]. Expression levels of proBDNF, mature BDNF, and BDNF proteins in the parietal cortex, cerebellum, liver, and spleen of patients with major depressive disorder, schizophrenia, and
bipolar disorder were measured by Yang et al. Interestingly, a negative correlation between mature BDNF in the parietal cortex and mature BDNF in the liver in all subjects was found [36]. Teillon et al. demonstrated that BDNF-TrkB signaling facilitated the development of metabolic disorders and liver damage. These were elicited by a high-fat diet [37]. Therefore, in mental disorders, the relationship between the brain and liver must be considered. Currently, the pathogenesis of NAFLD due to chronic psychological stress has not been fully elucidated. It could be multifactorial. Of the several possible mechanisms, the most important is that psychological stress could lead to hypothalamic-pituitary-adrenal (HPA) axis imbalances and inflammatory response.

**HPA axis**

The hypothalamic-pituitary-adrenal (HPA) axis is one of the major stress systems in the body. It has been described in several metabolic disorders [38]. The degree of HPA axis activation in patients with NAFLD is closely related to pathological changes in liver tissues [39]. During exposure to stressful events, the HPA axis is activated. Briefly, hypothalamic corticotropin-releasing hormone (CRH) is synthesized and released, increasing proopiomelanocortin (POMC) gene expression in the anterior pituitary gland. POMC is converted into adrenocorticotropic hormone (ACTH) and other melanocortin peptides, such as α-MSH. Subsequently, ACTH binds to melanocortin type 2 receptors of the adrenal cortex and stimulates glucocorticoid (GC) synthesis and secretion into the systemic circulation, exerting various physiologic effects. GC binding to glucocorticoid receptors (GCRs) in the hippocampus, CRH-secreting neurons of the hypothalamus, and the corticotrophs of the anterior pituitary gland inhibit the release of CRH and ACTH. These participate in the negative feedback regulation of the HPA axis [40-43].

Psychological stress is perceived by the HPA system [17]. First, the hypothalamus responds to stressors by secreting CRH. This triggers the pituitary gland to release adrenocorticotropic into the bloodstream. This, in turn, induces cortisol secretion from the adrenal cortex. Corticosteroids act on several organs and on areas of the brain through two types of receptors, mineralocorticoid receptors and GCRs, which have a specific and selective distribution in the brain. GC synthesis and secretion not only promote lipid production and accumulation but also enhance lipolytic hormone decomposition [44]. In the state of psychological stress, the hyperthyroid HPA axis continuously promotes the secretion of hormones in the adrenal cortex, thereby increasing corticosteroid levels. Moreover, mineralocorticoids, GC, and insulin resistance have a direct correlation [45]. A previous study found that, with the increase of corticosteroid levels, the degree of insulin resistance increased gradually [46]. Insulin resistance is the result of an imbalance between insulin production and glucose uptake, which affects insulin-stimulated glucose uptake at the adipose tissue and skeletal muscle levels, as well as resistance to insulin-mediated suppression of TG in adipose tissues [47, 48]. Insulin, one of the most important antilipolytic hormones in the human body, decreases the activity of lipolytic hormones in vivo that are relatively hyperactive, promoting hydrolysis of fatty acids and glycerol and inhibiting triglyceride hydrolysis. Consequently, functional activity decreases, resulting in rapid increases in body FFA [49]. Therefore, excessive GC content could lead to abnormal body fat decomposition, resulting in a large amount of FFA, increased blood glucose levels, and insulin resistance. The persistence of insulin resistance could lead to liver disorders and glucose and lipid metabolism disorders [49]. In NAFLD, insulin resistance is the core mechanism of hepatic steatosis [50]. A strong association between NAFLD and insulin resistance and MetS has been well-documented [51].

**Inflammation**

Evidence has shown that psychological stress may correlate with increasing incidence of MetS, inflammation, and NAFLD [52, 53]. Psychosocial stress has also been suggested to influence the course of hepatic inflammation by inducing tumor necrosis factor-alpha (TNF-α) production in rats [54]. Chronic psychological stress could induce or aggravate intrahepatic inflammatory responses. In addition to inflammatory factors secreted by the hippocampus, high levels of GC could stimulate immune cells to secrete inflammatory factors [55]. High levels of FFA could directly activate hepatocellular
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inflammatory bodies and aggravate inflammation [56]. In addition, oxidative stress plays an essential role in the development of NAFLD [57, 58]. Oxidative stress is an inflammatory reaction that occurs in parenchymal cells. It is induced by elevated reactive oxygen species through excessive aggregation of fat during intracellular triglyceride synthesis and transport dysfunction, due to insulin resistance in the liver [59]. Moreover, clinical studies have found that serum levels of SOD in patients with NAFLD are decreased significantly, while the MDA index is significantly higher. This suggests that oxidative stress is an important factor in the pathogenesis of NAFLD [60].

High GC levels after psychological stress could directly induce immune cell activation “NLRP3 inflammasome” [55, 61]. Some studies have shown that NLRP3 inflammatory body has a significant role in the course of NASH pathology [62]. Inflammatory factors mediate inflammation and activation of the liver inflammatory response. Knockout of NLRP3 (or inflammatory body-related molecules) or caspase 1 genes could inhibit high fat diet-induced insulin resistance, liver steatosis and inflammation, and early fibrosis [63]. Furthermore, NLRP3 inflammatory body has been recently found to regulate IL-1β maturation and secretion. In a mice NAFLD model, IL-1β knockout alleviated liver injury and slowed down the progression of NAFLD to NASH [63]. This indicates that IL-1β is a key inflammatory factor in NASH. Specifically, IL-1β could recruit inflammatory cells to the liver and induce fibrosis by activating hepatic stellate cells. In addition, IL-1β could induce TG accumulation in hepatocytes and, along with TNF-α, initiate hepatocyte death [63].

Therefore, psychological stress-induced inflammatory response, NAFLD, and the development of NAFLD to NASH are closely linked. Chronic psychological stress could cause “neurological-inflammatory-metabolic” disorders of the network. This, in turn, increases insulin resistance from multiple pathways, promoting the pathogenesis of NAFLD.

Conclusion

Chronic psychological stress may lead to an imbalance in the regulation of the HPA axis and abnormal secretion of hypothalamic hormones, resulting in glucose and lipid metabolism disorders. Moreover, it could lead to low grade inflammation, causing fat accumulation in the liver cells. It may lead to persistent inflammation of the liver, resulting in liver damage. Depression, anxiety, and other negative emotions are psychological responses to stress. They play a role in the liver’s inflammatory response and may induce NAFLD. Thus, psychological intervention in patients with NAFLD helps to promote the recovery of fatty liver and co-existing diseases. Mental health, therefore, has become a biological-psychological-social medical model-oriented medical system of concern.

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None.

Abbreviations

ACTH, adrenocorticotropic hormone; ALT, alanine transaminase; AST, aspartate transaminase; BD, bipolar disorder; BDNF, brain derived neurotrophic factor; CRH, corticotropin-releasing hormone; FFA, free fatty acid; GRs, glucocorticoid receptors; GC, glucocorticoid; GCR, glucocorticoid receptors; HPA, hypothalamic-pituitary-adrenal; HCC, hepatocellular carcinoma; IR, insulin resistance; LDL, low-density lipoprotein; MDA, malondialdehyde; MDD, major depressive disorder; MC, melanocortin; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAFL, non-alcoholic fatty liver; OR, odds ratio; POMC, proopiomelanocortin; SOD, superoxidedismutase; SZ, schizophrenia; TC, total cholesterol; TNFα, tumor necrosis factor alpha; TG, triglycerides.

Address correspondence to: Fafeng Cheng, School of Basic Medical Sciences, Beijing University of Chinese Medicine, 11 Beisanhuandong Road, Chao
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Yang District, Beijing 100029, China. Tel: 1381-0419194; E-mail: fafengcheng@gmail.com

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