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*Review Article*

# Impact of chronic psychological stress on nonalcoholic fatty liver disease

Shuang Zhang[1], Chongyang Ma[1], Xueqian Wang[1], Qingguo Wang[1], Wenting Song[2], Changxiang Li[1], Changming Zhai[3], Yuqing Qi[1], Shuning Fan[1], Fafeng Cheng[1]

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

stress [12-14]. 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 inteleukin-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

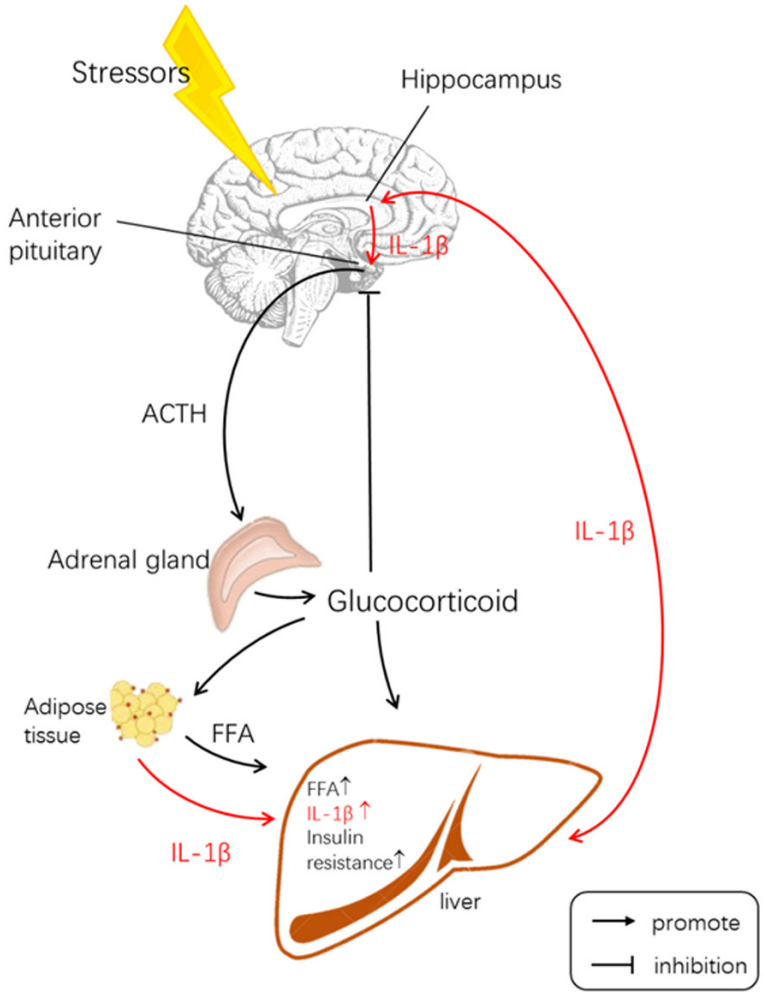


**Figure 1.** Chronic psychological stress results in a continuous activation of the "hypothalamic-pituitary-adrenal (HPA) axis", which leads to a high glucocorticoid level that interferes with nervous, metabolic, and immune systems. Specifically, chronic psychological stress could damage hippocampal neurons. Consequently, the hippocampus would lose its HPA axis inhibition capacity. The HPA axis would be in a sustained hyperactive state. The damaged hippocampus will release a large amount of IL-1β, thereby inducing inflammation. Moreover, chronic psychological stress could interfere with lipid metabolism. Subsequently, GC promotes the synthesis of intrahepatic fatty acids and accelerates the release of free fatty acids (FFA) by adipose tissue and the intermediates formed by abnormal lipid metabolism could lead to insulin resistance through related pathways. Hence, chronic psychological stress could induce or aggravate the intrahepatic inflammatory response. High levels of GC could induce the secretion of inflammatory factors by free immune cell in addition to the inflammatory factors secreted by the hippocampus. High levels of FFA could directly activate hepatocellular inflammatory body, thereby aggravating inflammation.

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 adrenocorticotropin 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

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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## Disclosure of conflict of interest

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, nonalcoholic 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

Yang District, Beijing 100029, China. Tel: 1381-0419194; E-mail: fafengcheng@gmail.com

## References


[1] Vernon G, Baranova A and Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011; 34: 274-85.

[2] Fan JG. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. J Gastroenterol Hepatol 2013; 28: 11-7.

[3] Gaggini M, Morelli M, Buzzigoli E, Defronzo RA, Bugianesi E and Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 2013; 5: 1544-1560.

[4] Chen Y, Varghese Z and Xiong ZR. The molecular pathogenic role of inflammatory stress in dysregulation of lipid homeostasis and hepatic steatosis. Genes Dis 2014; 1: 106-112.

[5] EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia 2016; 59: 1121-1140.

[6] Lomonaco R, Sunny NE, Bril F and Cusi K. Nonalcoholic fatty liver disease: current issues and novel treatment approaches. Drugs 2013; 73: 1-14.

[7] James W. What is an emotion? Mind 2007; 9: 188-205.

[8] Mcewen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007; 87: 873-904.

[9] Youssef NA, Abdelmalek MF, Binks M, Guy CD, Omenetti A, Smith AD, Diehl AM and Suzuki A. Associations of depression, anxiety and antidepressants with histological severity of nonalcoholic fatty liver disease. Liver Int 2013; 33: 1062-70.

[10] Cohen S, Kessler RC and Underwood GL. Strategies for measuring stress in studies of psychiatric and physical disorder. Measuring stress: A guide for health and social scientists. 1995.

[11] Elwing JE, Lustman PJ, Wang HL and Clouse RE. Depression, anxiety, and nonalcoholic steatohepatitis. Psychosom Med 2006; 68: 563-9.

[12] Mcewen BS, Gray JD and Nasca C. Redefining neuroendocrinology: stress, sex and cognitive and emotional regulation. J Endocrinol 2015; 226: T67-83.

[13] Kivimäki M and Kawachi I. Work stress as a risk factor for cardiovascular disease. Curr Cardiol Rep 2015; 17: 630.

[14] Surdea-Blaga T and Dumitraşcu DL. Depression and anxiety in nonalcoholic steatohepatitis: is there any association? Rom J Intern Med 2011; 49: 273-280.

[15] Jauch-Chara K and Oltmanns KM. Obesity–a neuropsychological disease? Systematic review and neuropsychological model. Prog Neurobiol 2014; 114: 84-101.

[16] Liu H and Waite L. Bad marriage, broken heart? Age and gender differences in the link between marital quality and cardiovascular risks among older adults. J Health Soc Behav 2014; 55: 403-23.

[17] Chida Y, Sudo N and Kubo C. Does stress exacerbate liver diseases? J Gastroenterol Hepatol 2006; 21: 202-8.

[18] Hänsel A, Hong S, Cámara RJ, von Känel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci Biobehav Rev 2010; 35: 115-21.

[19] Sergio G and Nicola M. Work stress and metabolic syndrome in police officers. A prospective study. PLoS One 2015; 10: e0144318.

[20] Chen X, Leng L, Yu H, Yang XL, Dong GH, Yue S, Chen JS and Tang NJ. Psychological distress and dyslipidemia in chinese police officers: a 4-year follow-up study in Tianjin, China. J Occup Environ Med 2015; 57: 400-5.

[21] Li C, Xing JJ, Shan AQ, Leng L, Liu JC, Yue S, Yu H, Chen X, Tian FS and Tang NJ. Increased risk of nonalcoholic fatty liver disease with occupational stress in Chinese policemen: a 4-year cohort study. Medicine (Baltimore) 2016; 95: e5359.

[22] Maraš JS, Kolundžija K, Dukić O, Marković J, Okanović P, Stokin B, Mitrovic D and Ivanović-Kovačević S. European review for medical and pharmacological sciences. Verduci 2011.

[23] Youssef NA, Abdelmalek MF, Binks M, Guy CD, Omenetti A, Smith AD, Diehl AM and Suzuki A. Associations of depression, anxiety and antidepressants with histological severity of nonalcoholic fatty liver disease. Liver Int 2013; 33: 1062-70.

[24] Stewart KE, Haller DL, Sargeant C, Levenson JL, Puri P and Sanyal AJ. Readiness for behaviour change in non-alcoholic fatty liver disease: implications for multidisciplinary care models. Liver Int 2015; 35: 936-43.

[25] Puustinen PJ, Koponen H, Kautiainen H, Mäntyselkä P and Vanhala M. Psychological distress predicts the development of the metabolic syndrome: a prospective population-based study. Psychosom Med 2011; 73: 158-65.

[26] Liu YZ, Chen JK, Zhang Y, Wang X, Qu S and Jiang CL. Chronic stress induces steatohepatitis while decreases visceral fat mass in mice. BMC Gastroenterol 2014; 14: 106.

[27] Cheng F, Ma C, Wang X, Zhai C, Wang G, Xu X, Jie M, Li C, Wang Z and Zhang X. Effect of traditional Chinese medicine formula Sinisan on chronic restraint stress-induced nonalcoholic fatty liver disease: a rat study. BMC Complement Altern Med 2017; 17: 203.

[28] Tsochatzis EA, Papatheodoridis GV and Archimandritis AJ. Adipokines in nonalcoholic steatohepatitis: from pathogenesis to implications in diagnosis and therapy. Mediators Inflamm 2009; 2009: 831670.
[29] Tarantino G and Finelli C. Pathogenesis of hepatic steatosis: the link between hypercortisolism and non-alcoholic fatty liver disease. World J Gastroenterol 2013; 19: 6735-43.
[30] Sies H. Oxidative stress: a concept in redox biology and medicine. Redox Biol 2015; 4: 180-3.
[31] Cabello-Verrugio C, Ruiz-Ortega M, Mosqueira M and Simon F. Oxidative Stress in disease and aging: mechanisms and therapies. Oxid Med Cell Longev 2016; 2016: 8786564.
[32] Macedo IC, Medeiros LF, Oliveira C, Oliveira CM, Rozisky JR, Scarabelot VL, Souza A, Silva FR, Santos VS and Cioato SG. Cafeteria diet-induced obesity plus chronic stress alter serum leptin levels. Peptides 2012; 38: 189-196.
[33] Czech B, Neumann ID, Müller M, Reber SO and Hellerbrand C. Effect of chronic psychosocial stress on nonalcoholic steatohepatitis in mice. Int J Clin Exp Pathol 2013; 6: 1585-93.
[34] Razzoli M, Domenici E, Carboni L, Rantamaki T, Lindholm J, Castrén E and Arban R. A role for BDNF/TrkB signaling in behavioral and physiological consequences of social defeat stress. Genes Brain Behav 2011; 10: 424-33.
[35] Jiang B, Wang F, Yang S, Fang P, Deng ZF, Xiao JL, Hu ZL and Chen JG. SKF83959 produces antidepressant effects in a chronic social defeat stress model of depression through BDNF-TrkB pathway. Int J Neuropsychopharmacol 2014; 18.
[36] Yang B, Ren Q, Zhang J, Chen QX and Hashimoto K. Altered expression of BDNF, BDNF propeptide and their precursor proBDNF in brain and liver tissues from psychiatric disorders: rethinking the brain-liver axis. Transl Psychiatry 2017; 7: e1128.
[37] Teillon S, Calderon GA and Rios M. Diminished diet-induced hyperglycemia and dyslipidemia and enhanced expression of PPARalpha and FGF21 in mice with hepatic ablation of brain-derived neurotropic factor. J Endocrinol 2010; 205: 37-47.
[38] Nieuwenhuizen AG and Rutters F. The hypothalamic-pituitary-adrenal-axis in the regulation of energy balance. Physiol Behav 2008; 94: 169-77.
[39] Konopelska S, Kienitz T, Hughes B, Pirlich M, Bauditz J, Lochs H, Strasburger CJ, Stewart PM and Quinkler M. Hepatic 11beta-HSD1 mRNA expression in fatty liver and nonalcoholic steatohepatitis. Clin Endocrinol (Oxf) 2009; 70: 554-60.
[40] Vale W, Spiess J, Rivier C and Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981; 213: 1394.
[41] Rivier C and Vale W. Modulation of stress-induced ACTH release by corticotropin-releasing factor, catecholamines and vasopressin. Nature 1983; 305: 325-327.
[42] Munck A, Guyre PM and Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev 1984; 5: 25-44.
[43] Bamberger CM, Schulte HM and Chrousos GP. Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. Endocr Rev 1996; 17: 245-61.
[44] Woods CP, Hazlehurst JM and Tomlinson JW. Glucocorticoids and non-alcoholic fatty liver disease. J Steroid Biochem Mol Biol 2015; 154: 94-103.
[45] Geer EB, Islam J and Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. Endocrinol Metab Clin North Am 2014; 43: 75-102.
[46] Sakamoto Y, Ogawa T, Ogawa M, Matsuo Y, Hashikawa N and Hashikawa N. [Effects of 15-day chronic stress on behavior and neurological changes in the hippocampus of ICR mice]. Yakugaku Zasshi 2015; 135: 151-8.
[47] Salmenniemi U, Ruotsalainen E, Pihlajamäki J, Vauhkonen I, Kainulainen S, Punnonen K, Vanninen E and Laakso M. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. Circulation 2004; 110: 3842-8.
[48] Sanyal AJ, Campbellsargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML and Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 2001; 120: 1183-1192.
[49] Saltiel AR. Insulin resistance in the defense against obesity. Cell Metab 2012; 15: 798-804.
[50] Day CP and James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology 1998; 114: 842-5.
[51] Birkenfeld AL and Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes. Hepatology 2014; 59: 713-723.
[52] Lee JH, Friso S and Choi SW. Epigenetic mechanisms underlying the link between non-alcoholic fatty liver diseases and nutrition. Nutrients 2014; 6: 3303-3325.

[53] Hoek-van den Hil EF, van Schothorst EM, van der Stelt I, Swarts HJ, van Vliet M, Amolo T, Vervoort JJ, Venema D, Hollman PC, Rietjens IM, Keijer J. Direct comparison of metabolic health effects of the flavonoids quercetin, hesperetin, epicatechin, apigenin and anthocyanins in high-fat-diet-fed mice. Genes Nutr 2015; 10: 469.

[54] Tjandra K, Sharkey KA and Swain MG. Progressive development of a th1-type hepatic cytokine profile in rats with experimental cholangitis. Hepatology 2000; 31: 280-290.

[55] Xu Y, Sheng H, Bao Q, Wang Y, Lu J and Ni X. NLRP3 inflammasome activation mediates estrogen deficiency-induced depression- and anxiety-like behavior and hippocampal inflammation in mice. Brain Behav Immun 2016; 56: 175-86.

[56] Yang G, Lee HE and Lee JY. Erratum: a pharmacological inhibitor of NLRP3 inflammasome prevents non-alcoholic fatty liver disease in a mouse model induced by high fat diet. Sci Rep 2016; 6: 26218.

[57] Sumida, Naito, Yoshikawa and Niki. Special issue on “oxidative stress and redox signaling in the;gastrointestinal tract and related organs” for free radical research; involvement of free radicals and oxidative stress in NAFLD/NASH. Free Radical Research 2013; 47: 869-880.

[58] Koek GH, Liedorp PR and Bast A. The role of oxidative stress in non-alcoholic steatohepatitis. Clin Chim Acta 2011; 412: 1297-305.

[59] Chen ZW, Chen LY, Dai HL, Chen JH and Fang LZ. Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease. Biomedical and Biotechnology 2008; 9: 616.

[60] Koruk M, Taysi S, Savas MC, Yilmaz O, Akcay F and Karakok M. Oxidative stress and enzymatic antioxidant status in patients with nonalcoholic steatohepatitis. Ann Clin Lab Sci 2004; 34: 57-62.

[61] Alcocer-Gómez E, Ulecia-Morón C, Marín-Aguilar F, Rybkina T, Casas-Barquero N, Ruiz-Cabello J, Ryffel B, Apetoh L, Ghiringhelli F, Bullón P, Sánchez-Alcazar JA, Carrión AM, Cordero MD. Stress-induced depressive behaviors require a functional NLRP3 inflammasome. Mol Neurobiol 2016; 53: 4874-82.

[62] Thomas H. NAFLD: a critical role for the NLRP3 inflammasome in NASH. Nat Rev Gastroenterol Hepatol 2017; 14: 197.

[63] Szabo G and Petrasek J. Inflammasome activation and function in liver disease. Nat Rev Gastroenterol Hepatol 2015; 12: 387-400.