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Editorial Board Member of *World Journal of Gastroenterology*, Fabio Grizzi, PhD, Head, Histology Core, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano 20089, Milan, Italy. fabio.grizzi@humanitasresearch.it

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Effective roles of exercise and diet adherence in non-alcoholic fatty liver disease

Wei Zhu

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Wei Zhu, School of Life Sciences and Technology, Tongji University, Shanghai 200092, China

Wei Zhu, Shanghai Xirong Information Science and Technology Co., Ltd., National Science and Technology Park, Tongji University, Shanghai 200092, China

Corresponding author: Wei Zhu, PhD, CEO, Postdoctoral Fellow, Researcher, School of Life Sciences and Technology, Tongji University, No. 1239 Siping Road, Yangpu District, Shanghai 200092, China. zhuwei8247@aliyun.com

Abstract

Non-alcoholic fatty liver disease (NAFLD) is characterized by symptoms of excessive fat accumulation and steatosis in the liver without alcohol intake in patients. The associated pathogenic mechanism is not completely understood and there are no specific drugs for patients with NAFLD. Exercise and diet adherence are the best options for the management of NAFLD patients. Questionnaire associated analysis models of adherence to these interventions are used to assess their effectiveness in the management of NAFLD patients using specificity, sensitivity, and so on. Studies have indicated that the relative ratio of NAFLD can be reduced by physical activity with diet control. In the future, the pathogenesis of NAFLD should be clarified with stratified efforts to develop appropriate drugs, and both exercise and diet adherence should be optimized using better questionnaire design and evaluation models for patients with NAFLD.

Key Words: Exercise and diet adherence; Non-alcoholic fatty liver disease; Delphi; Mediterranean diet; Physical lifestyle

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Core Tip: It is essential to reverse pathogenic syndromes before fibrosis occurs in patients with non-alcoholic fatty liver disease (NAFLD). Early diagnosis and appropriate interventions are important in NAFLD patients. Exercise and diet adherence may provide an effective treatment in patients with NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) affects approximately one third of the adult population worldwide, and is associated with a high risk of mortality when in combination with other serious syndromes such as cardiovascular diseases[1]. It is important to clarify various factors including environment, microbiome, metabolism, and genetics in predicting the progression and treatment outcome of NAFLD[2]. Obesity and insulin resistance can easily result in metabolic syndrome and inflammation, which could initiate the chronic progression of NAFLD to cirrhosis, and even hepatocellular carcinoma[3]. There are no specific drugs for NAFLD; therefore, it is meaningful to investigate the pathogenesis of NAFLD in order to provide information for drug development and other interventions. Hence, Zeng *et al*[4] evaluated the positive effect of exercise and diet adherence in patients with NAFLD as acceptable interventions.

The normal liver has the capacity to metabolize carbohydrates and fatty acids; however, fatty acids are commonly supplied or eliminated under abnormal conditions which results in endoplasmic reticulum stress and hepatocyte injury [5]. However, there is an important gap in the pathogenic mechanism between lipid metabolism symptoms and activated inflammatory progression of NAFLD[6]. One common explanation has indicated that gut microbiota disorder could trigger an abnormal immune microenvironment to mediate inflammatory responses in the liver in the presence of NAFLD. The lack of knowledge on the specific mechanism initiating NAFLD is hindering the development of effective drugs.

PATHOGENESIS OF NAFLD

NAFLD with insulin resistance has been shown to produce excessive fat accumulation and steatosis in the liver, which are classified as non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH), two distinct pathological conditions [7]. NAFLD is different from alcoholic liver disease which is associated with daily alcohol intake in patients. These diseases involve several different factors including costs, low predictive parameters, and risky liver biopsy, especially in patients aged > 50 years and those with type 2 diabetes mellitus[8]. In Figure 1, it can be seen that in hepatic steatosis, the uptake of free fatty acids, *de novo* lipogenesis, and fatty acid oxidation can result in excessive lipid accumulation in the liver. The outcomes of these metabolic syndromes in the liver can result in the export of very low-density lipoproteins into the blood circulation and the activation of inflammatory responses. In NAFLD, compensatory fatty acid oxidation and high lipid levels appear to damage subcellular functions of mitochondria, peroxisomes, and cytochromes, which also adversely affect other organs[9]. Additionally, liver oxidant/antioxidant imbalance can impair mitochondrial metabolism and possibly induce subsequent inflammation in NAFLD without a clear mechanism[10]. Despite advances in the pathogenesis of NAFLD being incomplete, one hypothesis of multiple hits is considered to explain the multiple insults in the development of NAFLD[11].

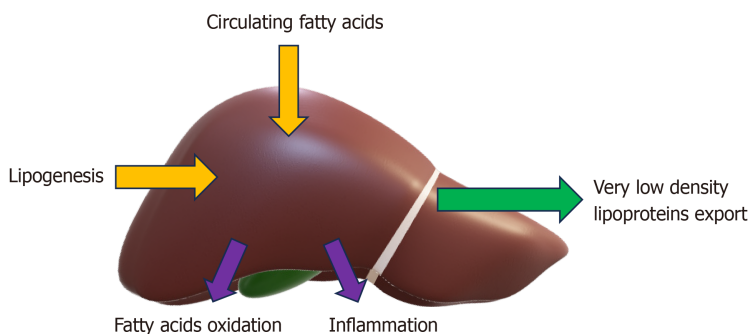


Figure 1 Dysregulation of liver function in non-alcoholic fatty liver disease.

EXERCISE AND DIET ADHERENCE IN NAFLD

Modifications of both physical activity and cognitive behavior were found to be beneficial in assisting patients with chronic diseases to overcome uncomfortable symptoms, and more than 60% of syndromes were inactive[12]. Urbanization in many Asian countries has promoted the prevalence of NAFLD due to sedentary lifestyle and overnutrition in around 25% of the population similar to many Western countries[13]. Zeng *et al*[4] reported that NAFLD

patients needed a positive change in their lifestyle, but few patients achieve improvements in weight reduction and persistent exercise and diet adherence. Therefore, the determination and perseverance in persistent exercise and diet adherence are critical in patients with NAFLD and chronic complications. Besides the role of exercise in these chronic diseases, an unhealthy diet such as excessive eating, smoking, and alcohol intake have a negative effect on life-expectancy and all-cause mortality rates[14]. Nutrition research has demonstrated that biological constituents have synergistic and/or antagonistic actions in human health beyond individual components[15]. An example is the Mediterranean diet which can prevent chronic diseases and premature mortality due to the dietary pattern and lifestyle in Mediterranean countries [16]. Clinically, many diseases including cardiovascular and neurodegenerative diseases and cancer have been associated with increasing age[16,17]. Similar to emerging non-communicative diseases, NAFLD commonly appears in diverse age groups especially in adults.

Although the accurate pathogenesis and standard treatment of NAFLD are not yet available, associated factors such as an unhealthy lifestyle is considered to elevate liver lipogenesis and microenvironment dysfunction. Hence, both the American Association for the Study of Liver Diseases and the National Institute for Health and Care Excellence guidelines recommended lifestyle modifications as the first choice for weight loss in patients with NAFLD[18,19]. Based on the results of Zeng *et al*[4], the efficacy of both exercise and diet adherence was high but only the specificity of diet adherence remained when compared to the control group. It is possible that diet adherence was easy to quantify and maintain, but sustaining exercise was difficult in patients aged > 50 years. In addition, instability of the composition of unsaturated fats could be improved by the high quantities of antioxidant compounds in foods. This study supported that complex food compositions were more beneficial than single or purified nutrients in the diet. The Mediterranean diet is recommended for NAFLD patients due to the presence of antioxidant compounds including polyphenols, carotenoids, fiber, and polyunsaturated fatty acids, which should be combined with physical activity[7]. It was reported that high adherence to the Mediterranean diet was associated with less liver damage and lower insulin resistance in patients with NAFLD[20]. Zeng *et al*[4] presented a similar conclusion on the effects of Mediterranean diet adherence, where exercise and diet adherence could greatly improve the clinical syndromes of patients with NAFLD.

REDUCED RATIO ANALYSIS OF NAFLD DUE TO MANAGEMENT

The Delphi method was used to collect opinions from experts with pooled intelligence and promote individual judgement on a particular field of research *via* a series of questionnaires[21]. In Table 1, this survey *via* different styles besides online interview was widely applied to gather primary data on patients with NAFLD and was displayed by Zeng *et al*[4] in their presentations[4,22-25]. The Pearson and Spearman correlation coefficients were used to analyze test-retest interval reliability, while exercise steps and reduced calorie intake were evaluated using the areas under the receiver operating characteristic curves. Different from these analysis methods, models of logistic, linear regression, and Cox proportional hazard were respectively applied to examine the odds, risk, and hazard ratios of combinations between physical activity and dietary adherence in NAFLD patients (Table 1). These ratios with confidence intervals were generally found to decrease after exercise and diet adherence in NAFLD patients. Hence, the establishment and validation of questionnaires with an appropriate analysis model are important for complete evaluation of the management of NAFLD patients.

Table 1 Reduced ratios of non-alcoholic fatty liver disease <i>via</i> exercise and diet adherence					
Ref.	Period	Data	Management	Model	Index
Heredia <i>et al</i> [22]	2017-2018	Online interview	Physical activity; dietary intervention	Multivariable logistic regression	Odds ratio (OR) = 0.65, 95% confidence interval (CI): 0.42-0.99; OR = 0.60, 95%CI: 0.44-0.84
George <i>et al</i> [23]	2002-2012	Questionnaire survey	Mediterranean diet	Binary logistic regression	OR = 0.99, 95%CI: 0.85-0.94; OR = 0.87, 95%CI: 0.80-0.96
Bullón-Vela <i>et al</i> [24]	55-75 years	Questionnaire survey	Mediterranean diet (high legume) + physical activity	Linear regression analyses (tertiles 2, 3)	Relative risk ratio = 0.45, 95%CI: 0.22-0.92; Relative risk ratio = 0.48, 95%CI: 0.24-0.97
Petermann-Rocha <i>et al</i> [25]	10.2 years	Questionnaire survey	Mediterranean diet	Cox proportional hazard	Hazard ratio = 0.76, 95%CI: 0.62-0.94

FUTURE PERSPECTIVES

The spectrum of NAFLD ranges from early steatosis to both inflammation and fibrosis in liver disease, while the stage of NAFLD is critical in diagnosis and treatment planning. Currently, liver biopsy is the standard method for diagnosis, but this is invasive and expensive for patients with NAFLD. It was reported that serum markers and a scoring system have been identified for determination of NAFLD and NASH[26]. Therefore, the investigation of novel serum markers should be encouraged *via* multi-omics techniques for the diagnosis of NAFLD.

Lifestyle modification involving diet and exercise is the first choice in the management of NAFLD patients. Questionnaires can be optimized by stratifying and subgrouping according to the diverse characteristics of patients with NAFLD in the clinic. In addition to these efforts, there are several drugs for both diabetes and obesity, and antioxidants such as

vitamin E, pioglitazone, and metformin that could be used to prevent the progression of steatosis and fibrosis may be beneficial in patients with NAFLD[27,28]. Also, several signaling molecules are considered to be involved in the progression of NAFLD by mediating lipid and sugar metabolism. One example is the transforming growth factor-beta 1 signaling pathway, which was found to be associated with the pathogenic progression of NAFLD[26,29]. Hence, molecules associated with signaling pathways are potentially important candidates in the diagnosis and treatment of NAFLD in the future.

CONCLUSION

The pathogenesis of NAFLD from early steatosis to fibrosis is critical for treatment of the disease, but has not yet been completely elucidated. As the underlying mechanism of NAFLD is incompletely understood, this has resulted in a lack of appropriate drug treatment. Exercise and diet adherence have become an effective lifestyle modification and will hopefully improve the optimization of NAFLD treatment.

FOOTNOTES

Author contributions: Zhu W designed the study, wrote the manuscript, and prepared the figure and table, in addition to other associated work.

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ORCID number: Wei Zhu 0000-0001-7523-7203.

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