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

Physical activity on NAFLD patients

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Abstract
NAFLD is shown by symptoms of excessive fat accumulation and steatosis in liver without alcohol intake in patients. Associated mechanism to induce pathogenesis remains not complete as well as no special drug is provided for clinical therapy in patients with NAFLD. Exercise and diet adherence is the best way for management of NAFLD patients in reality. Questionnaire associated analysis model of these adherence presented popular fashion to assess the effective value of management on NAFLD patients using specificity, sensitivity examination and so on. Progressions indicated that the relative ratio between physical activity with diet control and NAFLD syndrome could be reduced more or less. In the future, pathogenesis of NAFLD should be clarified with stratified efforts to develop corresponding drugs, as well as exercise and diet adherence also be optimized using better questionnaire designment and evaluated model 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 critical time to reverse pathogenic syndrome before fibrosis occurrence in patients with NAFLD. Early diagnosis and proper intervention should be used in the pathogenesis of NAFLD. Exercise and diet adherence with questionnaire provide an effective treatment to be evaluated in patients with NAFLD.

INTRODUCTION
Non-alcoholic fatty liver disease (NAFLD) affected about one third of whole mature population in the world, which was associated with high risk of mortality for combination of other serious syndrome such as cardiovascular diseases[1]. It was
important to clarify the different factors including environment, microbiome, metabolism and genetics of the natural history for predicting the progression and treatment outcome of NAFLD[2]. Usually, obesity and insulin resistance were easy to result in metabolic syndrome and inflammation, which could initiate the chronic progression of NAFLD to cirrhosis, and even hepatocellular carcinoma (HCC)[3]. There are not special drugs for NAFLD in clinic, as well as it is meaningful to investigate the pathogenesis of NAFLD for providing theory with the development of treatment drugs. Hence, Zeng et al has evaluated the positive effect of exercise and diet adherence on patients with NAFLD as acceptable interventions currently[4].

The capacity to handle carbohydrates and fatty acids displays certain in normal liver, but fatty acids are commonly supplied or disposed under abnormal status to provoke endoplasmic reticulum stress and injure hepatocytes[5]. However, there exists an important gap between lipid metabolic symptom and activated inflammatory progression of the NAFLD development without appropriate mechanism[6]. One common explanation indicated that gut microbiota disorder could trigger abnormal immune microenvironment to mediate inflammatory responses in the liver with NAFLD. Lack of specific function could extremely initiate NAFLD to produce the hindrance for developing effective drugs on abnormal liver clinically.

PROGRESSION OF PATHOGENESIS ON NAFLD

NAFLD with insulin resistance was indicated to produce excessive fat accumulation and present for steatosis in liver, which could be classified as non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) according to distinct pathological conditions[7]. NAFLD was differed from alcoholic liver disease which contained a daily quantity of alcohol intake in patients. There were several difficult circumstances including costs, low predictive parameters and risky liver biopsy of testing especially in patients with age > 50 and type 2 diabetes mellitus[8]. In Figure 1, knowledge of hepatic steatosis is pointed out that uptake of free fatty acids, de novo lipogenesis plus fatty acid oxidation can produce excessive lipid acquisitions in liver. Outcomes of these
metabolic syndromes of liver can export very low-density lipoproteins into blood circulation as well as inflammatory responses will be activated. In NAFLD, compensatory fatty acid oxidations and high lipid levels appeared to damage subcellular functions of both mitochondria, peroxisomes and cytochromes, which also adversely affected other organs[9]. Additionally, liver oxidant/antioxidant imbalance can impair metabolism of mitochondria and possibly induce subsequent inflammation of NAFLD without clear mechanism[10]. Despite advances on the pathogenesis of NAFLD remained incomplete to recognize, one hypothesis of multiple hits was considered to explore multiple insults for NAFLD production and accurately explained the generation of NAFLD[11].

EXERCISE AND DIET ADHERENCE FOR NAFLD

Modifications of both physical activity and cognitive behavior were beneficial to assist patients with chronic diseases for overcoming discomfortable symptoms, but more than 60% of syndromes kept inactive[12]. Past urbanization in many Asian countries promoted the prevalence of NAFLD via sedentary lifestyle and overnutrition for around 25% population like many Western countries[13]. Zeng et al mentioned that these NAFLD patients needed positively change their lifestyle but few patients achieve improvements to reduce weight with persistence using exercise and diet adherence[4]. Therefore, the determination and perseverance of persisting exercise and diet adherence is the critical point in patients with NAFLD plus chronic complications. Besides the role of exercise on these chronic diseases, unhealth diet such as excessive eating, smoking and alcohol displayed a critical effect on the life-expectancy and all-cause mortality rates[14]. Nutrition research has focused that biological constituent presented synergistic and/or antagonistic actions in human health beyond individual component[15]. An example of Mediterranean diet was provided to promote the prevention of chronic diseases and premature mortality by dietary pattern and lifestyle in Mediterranean countries[16]. Clinically, many diseases without communication including cardiovascular, neurodegenerative and cancer have been indicated to be
associated with age increases[16,17]. Like these emergingly non-communicative diseases, NAFLD is commonly appeared in diverse age stages especially in adults.

Realistic status remains not optimistic in accurate pathogenesis and standard treatment of NAFLD. Nevertheless, the associated factors such as unhealthy lifestyle is considered to be risky in elevating liver lipogenesis and microenvironment dysfunction. Hence, guidelines of both the American Association for the Study of Liver Diseases (AASLD) and the National Institute for Health and Care Excellence (NICE) recommended proper regulation in lifestyle to be first choice for weight loss and intervention on patients with NAFLD[18,19]. Based on the results in Figure 2 and 3 of Zeng et al demonstrated, the sensitivity of both exercise and diet adherence was high but only the specificity of diet adherence remained well compared to control group[4]. Maybe that diet adherence was easy to quantify and maintain, but levels and sustaining of exercise seemed hard to be acceptable and practice in patients with age > 50. In addition, instability of compositions with unsaturated fats could be protected by the high quantities of antioxidant compounds in foods. This recognition can support that complex compositions of foods are more beneficial than single or purified nutrients in the dietary intake. The Mediterranean diet was recommended to provide for NAFLD patients because antioxidant compounds including polyphenols, carotenoids, fiber and polyunsaturated fatty acids together with physical activity could be combined constantly[7]. It was reported that high adherence with Mediterranean diet was associated with less liver damage and lower degree of insulin resistance in patients with NAFLD[20]. Zeng et al presented the conclusion similar to effects of Mediterranean diet adherence, which exercise and diet adherence way could greatly intervene the clinical syndrome of patients with NAFLD[4].

REDUCED RATIO ANALYSIS OF NAFLD BY MANAGEMENT

The Delphi method was used to collect opinions from experts with pooled intelligence and promote individual judgement on a particular field research via a series of questionnaires[21]. In Table 1, this question survey via different styles besides computer interview were widely applied to gather primary data in patients with
NAFLD as well as Zeng et al displayed 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 characteristics curves (AUROC)[4]. Differed from these analysis methods, models of logistic, linear regression and cox proportional hazard were respectively applied to examine the adds, risk and hazard ratios of combinations between physical activity and dietary adherence in NAFLD patients (Table 1). These ratios with confidence interval (CI) were presented to decrease with more or less levels after exercise and diet adherence in NAFLD patients. Hence, establishment and validation of questionnaire with appropriate analysis model is important for complete evaluation of management on NAFLD patients.

FUTURE PERSPECTIVES

The spectrum of NAFLD ranged from early steatosis to both inflammation and fibrosis in liver disease, while the stage of NAFLD was critically discovered in the diagnosis and treatment. Currently, liver biopsy presents standard method for diagnosis, but this method is invasive harm and expensive cost for patients with NAFLD. It was reported that serum markers and score system was summarized for determination of NAFLD and NASH[26]. Therefore, novel serum markers should be encouraged to develop and investigate via multi-omics technique for the diagnosis of NAFLD.

Lifestyle modification of diet and exercise is the first choice in the management of NAFLD patients. Questionnaire of perspective cohort can be optimized via stratifying and subgroup according to diverse characteristics of patients with NAFLD in clinic. Besides these efforts, there were several drugs against both diabetic, obesity, and oxidants such as vitamin E, pioglitazone and metformin to be used in the progression of steatosis and fibrosis while these drugs could be potentially beneficial in patients with NAFLD[27,28]. By comparison, several signaling molecules are considered greatly to be involved in the progression of NAFLD via mediating lipid and sugar metabolism. Example of transforming growth factor-beta 1 (TGF-β1) signaling pathway was
critically presented in the pathogenic progression of NAFLD[26,29]. Hence, molecules associated signaling pathways are potential candidates for developing diagnosis and treatment of NAFLD in the future.

CONCLUSION
The pathogenesis of NAFLD from early steatosis to fibrosis is critically displayed in the treatment via associated intervention. The mechanism of NAFLD remains incomplete which results in the corresponding drugs to be lack of application. Exercise and diet adherence also become the effective lifestyle and will be hopefully improved using optimization in the treatment of NAFLD.

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