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Impact of lifestyle interventions on pathogenesis of nonalcoholic fatty liver disease

Ezzat WM. Lifestyle interventions and NAFLD
Abstract
This editorial builds on the article titled “Establishment and validation of an adherence prediction system for lifestyle interventions in non-alcoholic fatty liver disease” by Zeng et al. We carried out a critical examination of nonalcoholic fatty liver disease (NAFLD) pathogenesis and how lifestyle interventions could facilitate disease resolution, particularly highlighting that non-alcoholic steatohepatitis (NASH) is a severe form of NAFLD. Our discussion details that weight loss is a pivotal factor in disease outcomes: A 3%-5% reduction is enough for resolution in 50% of non-obese individuals, while a 7%-10% reduction achieves similar benefits in obese individuals, as demonstrated by MRS. Additionally, the editorial underscores that such lifestyle changes are instrumental not only in resolving NAFLD but also in reversing hepatic steatosis and inflammation. These insights, derived from the research, emphasize the critical role of personalized lifestyle modifications in halting the progression of NAFLD to NASH and even reversing fibrosis, thus offering a template for effective patient management.

Key Words: Nonalcoholic fatty liver disease; Non-alcoholic steatohepatitis; Diet; Physical activity; Life style

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Core Tip: Nonalcoholic fatty liver disease (NAFLD), closely linked to metabolic disturbances, is a progressive, chronic liver condition whose prevalence escalates with age. NAFLD elevates the mortality risk associated with liver-related illnesses, cardiovascular disease, and various cancers. Effective lifestyle interventions have been demonstrated to not only resolve NAFLD and its severe form, non-alcoholic steatohepatitis, but also to reverse fibrosis, underscoring the significant impact of lifestyle on disease prognosis.
INTRODUCTION

This editorial comments on the article titled “Establishment and validation of an adherence prediction system for lifestyle interventions in non-alcoholic fatty liver disease” by Zeng et al[1]. Nonalcoholic fatty liver disease (NAFLD) represents a major public health challenge, characterized as a dynamic and progressive metabolic liver disease intricately linked to metabolic disturbances. Recent statistics from 2016 to 2019 indicate a global prevalence of NAFLD at 38% among adults and approximately 10% among children and adolescents[2], with the highest recorded rates in the Middle East at 32%. The interconnection of NAFLD with the escalating worldwide epidemics of obesity and type 2 diabetes suggests that its prevalence will continue to rise[3]. The disease spectrum of NAFLD ranges from simple steatosis to more severe forms such as non-alcoholic steatohepatitis (NASH), advancing to liver fibrosis, cirrhosis, and potentially, hepatocellular carcinoma and liver failure. Notably, NASH is recognized as a particularly severe manifestation of NAFLD. Epidemiological data also show a concerning age-related increase in NAFLD prevalence, starting from 3% in children to over 40% in individuals older than 70 years old[4]. Complications from NAFLD contribute significantly to increased mortality risks associated with liver-related diseases, cardiovascular conditions, and malignancies[5]. Additionally, NAFLD impacts negatively on health-related quality of life, work productivity, and imposes a substantial economic burden due to increased healthcare demands[6]. Despite these implications, awareness among healthcare providers, patients, and policymakers remains insufficient[7]. Studies have shown that significant lifestyle-induced weight loss - ranging from 5% to more than 10% of body weight - can effectively resolve NAFLD and even reverse NASH and fibrosis. The impact of lifestyle changes varies with baseline body mass index (BMI), with non-obese individuals requiring less weight loss than their obese counterparts to achieve similar therapeutic outcomes[8].

PATHOGENESIS OF NAFLD
The pathogenesis of NAFLD and its progression to NASH has historically been explained by the “2-hit” hypothesis, initially proposed by Day and James[9]. The first hit involves hepatic triglyceride (TG) accumulation, increasing the liver’s vulnerability to subsequent insults. The second hit includes factors like oxidative stress, mitochondrial dysfunction, and the adverse effects of inflammatory cytokines and adipokines, leading to the development of steatohepatitis and fibrosis[10]. However, recent studies challenged this model by suggesting that free fatty acids (FFAs) themselves, not TG, may instigate liver damage through their lipotoxic effects. These findings indicate that FFAs elevate oxidative stress and activate inflammatory pathways, potentially offering protection against lipotoxicity, contrary to the earlier belief that TG accumulation was solely harmful[11]. This shift in understanding has given rise to a revised “2-hit” hypothesis, where the accumulation of FFAs constitutes the primary hit, sufficient to induce liver damage, with the toxicity varying among different FFA species[12].

HEPATIC FAT ACCUMULATION
The balance between lipid input and disposal determines the hepatic lipid content[13]. Sources of lipid input include lipolysis of adipose tissue, dietary fat consumption, and de novo lipogenesis in the liver[14]. Research indicates that the primary mechanisms for excessive hepatic TG accumulation involve increased liberation of FFAs from adipose tissue and heightened production of FFAs within the liver. Conversely, the disposal of lipids through β-oxidation and export via very-low-density lipoprotein is generally less affected[15]. Under normal conditions, insulin regulates fat storage by inhibiting the activity of hormone-sensitive lipase (HSL), an enzyme that releases FFAs from adipose tissue. However, in the state of insulin resistance, insulin’s ability to suppress HSL is compromised, leading to increased lipolysis and subsequently greater contributions of FFAs to hepatic TG accumulation[15].

HEPATIC INFLAMMATION IN NASH
Hepatic inflammation is a defining characteristic of NASH, representing the critical “second hit” in the 2-hit hypothesis model of disease progression. In NASH, this inflammatory response is markedly more severe compared to simple steatosis. Studies have highlighted significant elevations in pro-inflammatory cytokines and chemokines such as tumor necrosis factor-alpha (TNF-α), nuclear factor kappa B, and interleukin 6 in patients with NAFLD. Specifically, levels of TNF-α and monocyte chemotactic protein-1 are notably higher in NASH, while adiponectin, an anti-inflammatory mediator, is reduced. These biochemical changes underscore the enhanced inflammatory activity in NASH and differentiate it from less severe forms of NAFLD.[16]

OXIDATIVE STRESS AND NAFLD DEVELOPMENT
The connection between oxidative stress and the development of NAFLD is well-established in both human and animal studies.[17] In NAFLD, the hepatocytes often face an overwhelming influx of FFAs, which predominantly drives beta oxidation. This process results in the excessive production of reactive oxygen species (ROS), thereby inducing oxidative stress and triggering inflammatory pathways. Notably, the enzyme cytochrome P450 2E1 (CYP2E1), crucial for ROS production, is found to be elevated in both human and animal models of NASH. Furthermore, specific overexpression of CYP2E1 in hepatocytes leads to increased oxidative and nitrosative stress, highlighting its significant role in exacerbating NAFLD and its more severe form, NASH.[12]

THE IMPACT OF DIETARY FACTORS ON NAFLD
Emerging research highlights the significant role of diet in the development and management of NAFLD.[18] Diets high in calories, particularly those rich in saturated and trans fats, cholesterol, and fructose, are known to promote central adiposity, visceral fat, and consequently, NAFLD. Notably, the prevalence of NAFLD has been linked to Western dietary patterns, which remain influential regardless of gender, family income, or physical activity levels.[19] Conversely, adhering to a “Healthy dietary pattern” - characterized by high intake of fruits, vegetables, nuts, olive oil,
low-fat dairy, fish, and garlic - has been associated with a significantly reduced risk of NAFLD, as proved by Salehi-Sahlabadi et al. who concluded that this relationship holds true across various demographics, including age, gender, BMI, and energy intake levels, underscoring the protective role of antioxidant-rich and fiber-dense foods. Specifically, antioxidants like vitamins A, E, and C, prevalent in fruits and vegetables, protect against oxidative stress and NAFLD. Additionally, the omega-3 fatty acids found in fish are effective in lowering total cholesterol and mitigating NAFLD risk. Similarly, the Mediterranean diet, which includes ample fresh fruits, vegetables, nuts, moderate dairy and fish, and minimal intake of red meat and processed foods, has also demonstrated protective effects against NAFLD in numerous studies.

PHYSICAL EXERCISE AND NAFLD MANAGEMENT

Current health guidelines recommend at least 150 min per week of moderate to vigorous physical activity or achieving 10000 steps per day to prevent cardiovascular diseases and reduce the risk of metabolic disorders such as obesity, diabetes, and NAFLD. Despite these recommendations, many individuals fail to meet these targets, contributing to the rising prevalence of these conditions.

A recent longitudinal study involving 5860 adults investigated the impact of physical activity on NAFLD’s natural progression. The study found that individuals without NAFLD, who were consistently active or increased their physical activity, had a lower risk of developing the disease compared to those who remained inactive, regardless of their BMI. Furthermore, for participants with NAFLD at the start of the study, maintaining or initiating physical activity led to an improvement in NAFLD status, notably the resolution of hepatic steatosis as observed on ultrasonography.

Researches also indicates a dose-response relationship between physical activity and NAFLD, affecting both the prevalence and severity of the disease. Increasing daily physical activity is beneficial, and incorporating multiple short bouts of activity throughout the day has been suggested as an effective and possibly more achievable approach for individuals with NAFLD. This strategy can be as
beneficial as longer periods of continuous exercise and may fit better into the lifestyles of those managing this condition[20].

**CLINICAL IMPLICATIONS**
Enhancing public awareness about NAFLD is crucial. Physicians play a key role in this effort by clearly defining NAFLD, explaining its risk factors and complications, and emphasizing the significant impact of lifestyle modifications on reducing its incidence and improving treatment outcomes. It is critical to advise patients against extreme dietary restrictions and intense physical activity regimens aimed at rapid weight loss. Instead, advocating for moderate and consistent dietary changes combined with regular physical activity is recommended. Such balanced approaches are more likely to protect against the mortality associated with metabolic disorders and ensure long-term adherence and health benefits.

**CONCLUSION**
NAFLD has rapidly become the most prevalent liver disease worldwide, affecting not only adults but also an increasing number of children and adolescents. Despite the availability of medical treatments, lifestyle interventions such as diet and physical activity adjustments remain the most effective methods for managing NAFLD. Proactively promoting awareness and understanding of NAFLD risk factors can significantly reduce, and even reverse, hepatic steatosis and inflammation. This approach not only addresses the symptoms but also targets the underlying causes of NAFLD, offering a sustainable solution to this growing health concern.
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