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Comprehensive Study and Triggering Factors of Alcoholic and Non-Alcoholic Fatty Liver

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Abstract

Over the past few years, fatty liver disease has turned out to be a rather widespread phenomenon and has become a serious issue with the global population nowadays. It comprises alcoholic fatty liver disease and non-alcoholic fatty liver disease, which develop under the influence of various initiating factors, though frequently follow similar pathologies. The overloading of lipids in the hepatocytes in most cases will be the first sign of the disease, which may progress further to inflammation, fibrosis, and cirrhosis in case the culprits are not removed. In this review, emphasis of investigation has been laid on the key biological and lifestyle issues which provoke the onset of fatty liver disease. Genetic pre-disposition, resistance to insulin, and impaired lipid metabolism denote a significant contribution to the role of enhancing hepatic fat accretion. Moreover, oxidative stress and inflammatory reactions provide the factors of hepatocellular destruction and promote the course of the disease. Other lifestyle choices include chronic alcohol consumption, poor nutrition, sedentary physical behaviors, being overweight, psychological stress, smoking exacerbates liver damage and are significant sources of disease severity. It is worth noting that fatty liver disease usually goes unnoticed in its initial stages where the conditions can be reversed. The understanding of the interacting risk factors about alcoholic and non-alcoholic fatty liver disease could be enhanced, which could aid in an early intervention measure and help mitigate the long-term liver-related complications.

Keywords: Fibrosis, inflammation, lipid metabolism, liver disease, non-alcoholic fatty liver, smoking

INTRODUCTION

The liver is at the center stage in promoting metabolic homeostasis due to its participation in helping the body in the metabolism of nutrients, detoxification processes, lipid regulation and immune modulation [1]. As a result of this versatile activity, the liver is subjected to constant stresses on metabolic processes, toxication, and inflammatory factors. The long-term or repeated exposure to these kinds of insults can interfere with the normal functioning of the hepatic and cause it to start to undergo pathological changes which can be transformed through the course of time into chronic liver disease [2].

Fatty liver disease is a type of disorder that is one of the most frequent chronic disorders of the liver and is associated with the imposition of many lipids in the hepatocytes [3]. Fatty liver disease can be categorized among themselves as alcoholic fatty liver disease and nonalcoholic fatty liver disease based on the chief cause of the condition. Where alcoholic fatty liver disease is caused by the chronic alcohol usage, non-alcoholic fatty liver disease is combined largely with the metabolic discontinuity including obesity, insulin resistance, lipidemia and sedentary way of life [4]. Although the two conditions differ in their etiology, both have similar pathological characteristics, and they could follow the same stages of liver damage.

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Fatty liver disease can be non-symptomatic and may take very long to manifest itself in its early stages. Simple hepatic steatosis is normally termed as a reversible scenario but continued exposure to underlining threats might initiate an inflammatory cascade, resulting in steatohepatitis, fibrosis and finally cirrhosis [5]. Liver disease is known to lead to high morbidity, liver failure and hepatocellular carcinoma at the advanced stages hence early diagnosis and treatment of the disease is of paramount importance.

A recent shift in lifestyle, such as the high intake of high-density diets, lack of exercise, psychological stress, smoking, and drug use, has led to a fast prevalence of both alcoholic and non-alcoholic fatty liver disease in many countries of the world [6]. Alongside lifestyle-dependent factors, there are genetically predetermined and metabolically susceptible individuals to respond to hepatic stress, which explains the differences in severity and progression of the disease in individuals who experience it. Biological susceptibility interacts with environmental exposure to contribute to the results of the diseases.

Through its multifactorial approach, there is a need to gradually understand the triggering factors and progression of a fatty liver disease. The purpose of this review is to give a unified presentation of the biological and lifestyle determinants, as well as the developmental pathogenesis of both alcoholic and non-alcoholic fatty liver disease, with special focus on common pathogenic pathways, interactions of risk factors, and prevention measures [7]. This knowledge can be used in approaches towards early intervention and may also help to decrease the burden of chronic liver disease in the long term [8].

OVERVIEW OF LIVER DISEASES

Liver diseases are a wide array of pathological conditions that vary in severity, etiology and presentation. Out of them, fatty liver disease, hepatitis, fibrosis, and cirrhosis are some of the important stages in the development of chronic liver injury. The first and most frequent manifestation is usually the fatty liver disease which is defined by extreme triglyceride accumulation among the hepatocytes. In fact, this disorder can be benign, but persistence of the exposure to harmful factors can facilitate inflammation and hepatocellular injury [9].

Hepatitis is characterized by inflammatory alterations of the liver and can occur because of infectious, toxic, metabolic, or immune induced diseases [10]. Should hepatic inflammation proceed to be chronic, response to wound-healing may occur to bring about fibrosis, which is characterized by the abnormal accumulation of extracellular matrix constituents [11]. Progressive fibrosis has distorted liver architecture and liver functions and at the severe stages, cirrhosis occurs; cirrhosis is irreversible disorders that are characterized by portal hypertension, liver failure and hepatocellular carcinoma increases [12].

Discovery of liver disease can be carried out by alcoholic and non-alcoholic factors. Alcoholism is already a known cause of liver damage, and this has its effect due to the toxic effects and oxidative stress or inflammatory processes [13]. Non-alcoholic liver diseases on the other hand are becoming more associated with metabolic devastations like obesity, insulin resistance, dyslipidemia and sedentary living styles [14]. Alcoholic and non-alcoholic liver diseases tend to share common pathologic mechanisms even though they are initiated by different factors, and severity as well as the evolution of these diseases are largely overlapping (Figure 1) [15].

Significance of Liver Damage at an Early Age

The silent progression of liver disease, especially at the initial stages, is one of the most difficult [16]. Fatty changes in the liver with mild inflammatory alterations often succeed without leaving any clinical signs, and the disease is progressing without paying attention. This results in numerous patients being diagnosed when they have already caused substantial liver damage, thereby limiting the options available as a form of treatment, as well as the risk of having complicated scenarios in the long term [17].

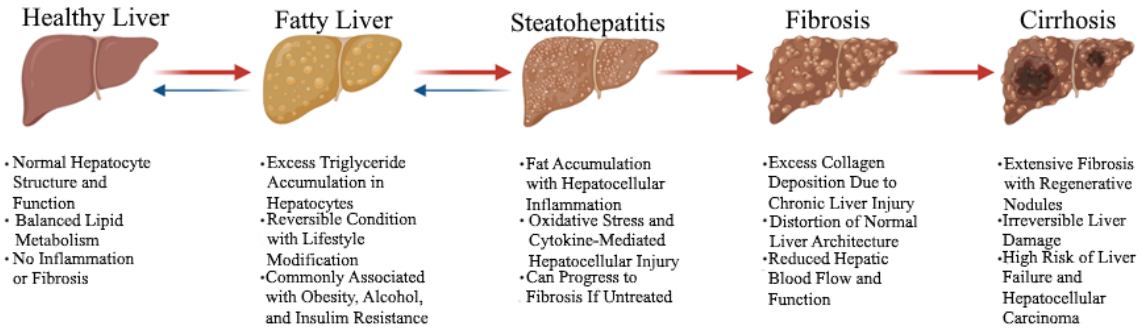

Figure 1. Progression pathogenesis of fatty liver disease demonstrating normal liver to cirrhosis with emphasis on reversible and irreversible stages.
Source: The author developed it according to the published literature [2, 6].

Noteworthy, liver is potentially reversible early in case it is detected before the development of severe fibrosis. Lifestyle change, dietary changes, weight loss, and alcohol intake can help to restore normal liver activity in most of the instances [18]. Timely diagnosis can also be used to manage underlying risk factors that metabolically and behaviorally may cause it to proceed into a state of irreversibility like cirrhosis [19]. All these reasons make it clear that greater attention should be paid to the early recognition, screening, and awareness of contributory factors in the context of the overall burden of chronic liver disease reduction [20].

BIOLOGICAL FACTORS IN THE DEVELOPMENT OF LIVER DISEASE

Liver disease progression cannot be attributed only to the external impact exposures like alcohol intake or unhealthy lifestyle habits. There are significant variations in clinical outcomes of many people who are exposed to similar environmental conditions, which means that there are determinant biological factors on disease susceptibility and progression [21]. The genetic predisposition, the efficiency of metabolic processes, and the stress-response systems of the cells combine to affect how the liver responds to the overwhelming of the metabolic demands and the attack of liver-toxic substances [22]. In the event of a defect in these adaptive mechanisms, hepatic injury is increased in probability, and an accelerated progression of the disease is observed [23].

The liver is a metabolically active gland that constantly controls lipid storage system, glucose metabolism and inflammatory signaling [24]. These highly regulated mechanisms breakdown can lead to the increase in lipid levels, dysfunction and the inflammation processes. These biological imbalances are the basis of fatty liver disease development and define whether the damage on the liver will be reversible or will lead to chronic liver damage [25].

Genetic and Metabolic Susceptibility

Genetic predisposition is a significant factor that controls the vulnerability of people to alcoholic as well as non-alcoholic fatty liver disease [26]. Alterations in genes that mediate lipid metabolism, insulin signal transduction and inflammatory controls may modify fat management in the liver and cellular reaction to stress [27]. Such genetic variations can be used to explain why certain individuals develop fatty liver disease or progress to advanced stages in very short time although people may be poorly exposed to known risk factors, among other things at the same time others are almost unaffected [28].

Metabolic impairment, specifically insulin resistance, is also fundamental in the hepatic fat build-up [29]. A defective signal of insulin enhances cellular lipolysis in the peripheral fat, and this elevates the circulation of free fatty acids taken up by the liver. Simultaneously, insulin resistance stimulates novo lipogenesis in hepatocytes in exchange of fatty acid oxidation and lipid exportation [30]. The resulting effect of this combination is too much deposition of triglycerides, which is the characteristic of hepatic steatosis [31].

There is a tendency of metabolic imbalance and genetic susceptibility to work together [32]. The presence of genetic variants in people, which modulate lipid storage or inflammatory mechanisms can lead to exaggerated hepatic floatation in outbreak of anthropometric obesity and elevated intake of nutrients. Such genetic-metabolic interplay leads to perpetuated cellular stress, rendezvous of hepatocytes to damage, as well as enhances chances of a progression of simple steatosis to steatohepatitis and fibrosis [33].

Constant overload on the metabolism also interferes with intracellular signaling pathways controlling glucose and lipid homeostasis [34]. Chronic hyperinsulinemia and high levels of free fatty acids induce constant metabolic stress to the hepatocytes causing strain on the mitochondria and poor functioning of the cells. These changes accomplish this by reducing the ability of the liver to recover and increasing the ability to sustain oxidative and inflammatory damage, ultimately increasing the speed at which disease progresses [35].

Oxidative Stress and Inflammation

Oxidative stress is an intrinsic process in the pathogenesis of hepatocellular injury in alcoholic and non-alcoholic liver diseases. It occurs during excessive production of reactive oxygen species surpassing the antioxidant protective capacity of the liver [36]. The large contributors to excessive production of reactive oxygen species in hepatocytes include alcohol metabolism, lipid overload, and mitochondrial dysfunction [37].

B-oxidation and electron transport chain dysfunction, in addition to oxidative stress, is further enhanced in fatty liver disease [38]. The surplus reactive oxygen species destroys the cell membrane, proteins, and nucleic acid and interrupts the normal functioning of hepatocytes, which leads to cell death. This oxidative condition disrupts hepatic homeostasis and is an important stimulus to inflammatory events in the liver [39].

Inflammation and oxidative stress are the two closely interrelated processes. Calculus causes an augmentation of oxidative burdens environmentally to resident immune cells and instigates the emittance of pro-inflammatory cytokines and chemokines [40]. These intermediaries sustain the hepatocellular damage, stimulate the recruitment of immune cells, and maintain a state of persistence, chronic inflammatory tissue in hepatic tissue [41].

The long-lasting inflammation also leads to the activation of hepatic cells of the stellate, which is the key factor in fibrogenesis [42]. These cells become activated and secrete a plethora of extracellular matrix components to the extent that they cause fibrosis and abnormality of normal liver architecture [43]. It is continuous oxidative stress and inflammatory response that, therefore, promotes the process of reversible liver injury to progressive fibrosis and cirrhosis [45].

Altogether, genetic vulnerability, metabolic dysgenesis, oxidative stress, and inflammation constitute complex biological networks which are foundational in the development and pathogenesis of alcoholic and non-alcoholic fatty liver disease. Knowledge of such biological processes is crucial in determining those individuals at high risks and also in coming up with proper preventive and therapeutic interventions [46].

LIFESTYLE-RELATED FACTORS THAT CAUSE LIVER DISEASES

The lifestyle factors are significant in the onset and development of both alcoholic and non-alcohol fatty liver disease. Such factors tend to co-exist with the influence of biological susceptibility, aggravating the metabolic tension and inflammatory processes in the liver [47]. The risks that are lifestyle-related are highly manipulable unlike the ones that have a genetic basis, and therefore, should be targeted by prevention and treatment of the disease [48]. Hepatic health and severity of diseases are influenced by the patterns of alcohol use, diet, physical activity, psychological stress, smoking, and use of other substances [49].

Diet and Alcohol Consumption

The long-term use of alcohol is a long-known cause of liver damage and is still a prime cause of morbidity in the liver on the global scene. The metabolism of alcohol in hepatocytes produces toxic and toxic metabolites, including acetaldehyde and increases the excessive production of reactive oxygen species leading to oxidative stress and direct hepatocellular damage [50]. Lipid metabolism is also disturbed by repeated exposure to alcohol that stimulates the production of triglycerides and reduces the ability to export lipids resulting in fat deposition in the liver. In the course of time, these alterations might lead to alcoholic steatohepatitis, fibrosis, and cirrhosis as well as steatosis [51].

Dietary habits alone have great impact on the liver's health. The diets, which are rich in saturated fatty acids and refined carbohydrates and addition of sugars, have a great correlation with the hepatic fat accumulation and the resistance of insulin. Overeating of calories leads to the de novo lipogenesis process and saturates hepatic lipid processes. Conversely, malnourished diets with lack of essential antioxidant, and micronutrients reduce the hepatic defence systems making the body vulnerable to oxidative and inflammatory damage [52]. In combination with improper nutrition habits and alcohol intake, the liver damage is enhanced, and the development of the diseases will gain speed [53].

Obesity and Physiological Inactivity

Obesity is also among the most significant risk factors in non-alcoholic fatty liver disease and is closely observed to be associated with metabolic syndrome. When there is excess adipose tissue especially visceral fat, it causes more free fatty acids and proinflammatory cytokine to be released into the bloodstream and directly transported to liver [54]. This encourages hepatic lipid deposition, inflammation, and insulin resistance establishing a metabolic condition that supports the disease progression [55].

Physical sedentary lifestyle also complicates all these metabolic disorders. Sedentary lifestyle causes less expenditure of energy and weight gain, as well as a decrease in insulin sensitivity and impairment of mitochondrial activity [56]. Physiological inactivity reduces the oxidation of fatty acids and increases lipid metabolism in hepatocytes, thus supporting the occurrence of hepatic steatosis. Research has always revealed that with less physical activity there is more content of liver fats regardless of the body weight [57].

Obesity and physical activity comorbidity have an enormous effect of increasing chances of simple fatty liver evolving into non-alcoholic steatohepatitis and fibrosis. Critically, even when a modest weight loss is actually attained via modification in dieting and normal physical exercises, liver enzyme levels are shown to improve and a decrease in the amount of hepatic fat content is indicated, which underscores the reversibility of the initial stages of the disease [58].

Psychological Stress, Smoking, and Substance Use

Psychological stress has come out as a significant yet neglected cause of liver disease. Excessive stress is linked to prolonged stimulation of the hypothalamic-pituitary-adrenal axis accompanied by an increase in cortisol, which interferes with glucose and lipid metabolism [59]. The possible effects of these hormonal changes are indirect encouragement of hepatic fat and aggravation of insulin resistance. Moreover, stress can typically affect unhealthy habits including poor nutritional habits, drinking, and lack of exercise, which present an even greater threat of liver damage [60].

Cigarette smoking was identified to promote liver disease through heightening oxidative stress and hepatic inflammatory signaling in liver tissue [61]. Smoking toxins increase the lipid peroxidation and can modulate the effect of alcohol and metabolic risks factors in hepatotoxicity [87]. Clinical and epidemiological research shows that smoking is accompanied by an increase in disease severity and acceleration of fatty liver disease especially when it is combined with alcohol consumption or obese [62].

Additional metabolic and toxic load on the liver occurs because of the use of drugs that hepatotoxic drugs and having been exposed to hepatotoxic drugs. Some chemicals can block the action of hepatic

detoxification pathways and enhance the oxidative damage, which promotes the evolution of the disease [63]. The subsequent pressure in parts of smoking and substance use highlights the presence of a multifactorial and interactive nature of lifestyle-related liver disease along with the necessity to embed end-wide tackling of preventive provisions.

RISK FACTOR AND PREVENTION INTERACTION

Fatty liver disease is hardly caused because of a singular etiological pathway. Rather, it is a product of a complex and dynamic interaction of biological disposition and exposures in relation to lifestyle over an extended period [64]. Combined genetic predisposition, metabolic anomalies, nutrition, alcohol use, physical lack of activity and behavioral have cumulative pressure on the hepatic cells [65]. The interplay between these factors does not only contribute to the increase of risk of developing diseases but also defines the speed of disease progression and clinical outcomes intensity.

With the interactions being important, analyzing these interactions is important since in most cases, there are those who are vulnerable to the effects of several and one risk factors, and it is likely that their liver may be affected more quickly than those who are vulnerable to one of the factors. According to this multifactorial model, it is evident why there is so much diversity in the development of the disease, which may or may not progress to benign steatosis or severe fibrosis and cirrhosis in various individuals [66].

Interaction of Multiple Risk Factors

Metabolic deviations in the form of insulin resistance, obesity and dyslipidemia expose the liver to a highly susceptible hepatic environment [67]. Under these circumstances, the liver portrays a greater lipid build-up, dysfunction of the mitochondria as well as an amplified oxidative stress. These metabolic disturbances are majorly enhanced by external influences like alcohol intake leading to hepatocellular damage [68].

Even light drinking has been exemplified to worsen underlying livers amongst patients who had innate metabolic risks. This promotes oxidative stress and inflammatory signaling pathways which together with insulin resistance and lipid overload stimulate disease progression. It is especially applicable to the current populations where metabolic syndrome and alcohol consumption are often comorbid [69].

Eating habits and lack of physical activity also add to this kind of synergy. The surplus of calories and decreased energy expenditure encourage the continuous low-grade inflammatory process and breaks the control of hepatic lipid homeostasis [70]. The changes promote the risk of toxic lipid intermediates accumulation in hepatocytes and predisposition to inflammatory damage and fibrogenesis [71].

The individual reaction to environmental and lifestyle factors is also altered by genetic vulnerability. Genetic polymorphs in lipid metabolism genes and inflammatory control could enhance hepatic fat deposition and fibrotic reactions in the presence of metabolic stress or alcohol [72]. As a result, genetically predisposed individuals might also develop diseases very fast despite having quite mild exposures to lifestyle factors.

All these factors together in a combination of metabolic, lifestyle, and genetic risk factors lead to a synergistic cascade of hepatocellular damage. This communication enhances the process of progression of simple steatosis to steatohepatitis, fibrosis and cirrhosis, highlighting the significance of tackling the multiple risk factors that interact and not individually (Table 1) [73].

Prevention and Lifestyle-Based Management

It is clear that preventive and management measures against alcoholic and non-alcoholic fatty liver disease need to be long-term and multifactorial as opposed to targeting a single risk factor [106]. As a major part of the contributing lifestyle-related determinants is modifiable, early intervention provides a massive potential to change the progression of the diseases and in most of the instances undo the hepatic damage [74].

Table 1. Biological and lifestyle risk factor interactions involved in the development and progression of alcoholic and non-alcoholic fatty liver disease.

Risk factor category	Specific factors	Pathophysiological mechanism	Impact on disease progression	Prevention / management strategies
Genetic factors	PNPLA3 variants, inherited metabolic disorders	Altered lipid handling and increased hepatic fat retention	Early steatosis, increased fibrosis risk	Early screening, lifestyle modification.
Metabolic factors	Insulin resistance, dyslipidemia	Increased free fatty acid influx and reduced lipid oxidation	Steatosis progressing to steatohepatitis	Weight reduction, metabolic control.
Oxidative stress	Reactive oxygen species, mitochondrial dysfunction	Lipid peroxidation and hepatocellular injury	Inflammation and fibrosis	Antioxidant-rich diet, alcohol avoidance.
Alcohol consumption	Chronic or excessive alcohol intake	Acetaldehyde toxicity and oxidative stress	Alcoholic steatohepatitis, cirrhosis	Alcohol abstinence, counseling.
Dietary factors	High-fat diet, refined carbohydrates, nutrient deficiency	Excess triglyceride accumulation and impaired hepatic defense	Fatty liver and inflammation	Balanced diet, calorie regulation.
Obesity And physical inactivity	Central obesity, sedentary lifestyle	Adipose tissue inflammation and insulin resistance	NAFLD progression and NASH	Regular physical activity, weight management.
Psychological stress	Chronic stress, elevated cortisol	Hormonal imbalance and metabolic dysregulation	Accelerated disease progression	Stress management, behavioral therapy.
Smoking and substance use	Cigarette smoking, drug abuse	Increased oxidative stress and inflammatory signaling	Synergistic liver injury	Smoking cessation, substance control.
Combined risk interaction	Obesity, alcohol use, genetics	Synergistic hepatocellular damage	Rapid fibrosis and cirrhosis	Integrated lifestyle-based management.

Source: Compiled by the author based on published literature [22, 25].

The prevention of alcohol-related liver disease is still based on alcohol moderation or total abstinence. The alcohol decreases hepatic oxidative stress, constrains an inflammatory reaction, and stops additional hepatocellular damaging. The progression rate of the disease in individuals, who have already liver dysfunctional record, is significantly higher on an ongoing alcohol intake, and abstinence has been reported to enhance the liver histology and clinical outcome [75].

The most important intervention that could be used in the prevention and management of non-alcoholic fatty liver disease is lifestyle modification. Food manipulation that lowers the consumption of calories and saturated fats, as well as refined carbohydrates, have proven their positive effects on liver fat level and insulin responsiveness. High fruit, vegetables, whole grain, and unsaturated fat diets are beneficial in enhancing the metabolic balance and decreasing the level of inflammatory load in the liver [76]. Other small steps of weight loss with diet changes have also been related to immense recovery in the liver enzymes and histological characteristics of fatty liver disease.

Regular exercise is very crucial in the prevention of liver diseases irrespective of weight loss. Exercise increases insulin sensitivity, fatty acid oxidation and decreases lipid hepatitis. Both aerobic and resistance training have been demonstrated to reduce the content of liver fats, as well as overall metabolic health, and as such, physical activity is a central figure in the lifestyle-based management strategies [77].

Early diagnosis and risk analysis are essential in preventive care, especially in the case of obese persons, metabolic syndrome, diabetes mellitus or a family history of liver disease. A timely diagnosis of fatty liver disease, as a disease, makes it possible to conduct early lifestyle counselling and monitoring and avoid the irreversible stages of the disease, including fibrosis and cirrhosis. Non-

invasive diagnostic devices and regular metabolic examination have significant influence on timely detection and the monitoring of the disease.

Besides diet and exercise, there are other related behavioral factors to tackle to improve the effects of prevention like smoking, getting stressed psychologically, and substance use. Smoking quit relieves oxidative stress, inflammatory signaling, and stress management approaches can be used to normalize the hormonal imbalance causing metabolic dysfunction. A patient-focused (integrated) strategy of lifestyle changes, behavioral counseling and clinical monitoring is thus vital to effective long-term management of fatty liver disease [78].

CONCLUSION

Fatty liver disease is a widespread health issue nowadays that is observed in the world among alcohol drinkers as well as the non-drinkers. Despite the fact that alcoholic and non-alcoholic fatty liver diseases are triggered by different agents, they tend to proceed through the same pathological path in the liver. The first stage of the disease is the accumulation of fats in hepatocytes and in most cases, it is reversible. Nevertheless, additional exposure to adverse metabolic and lifestyle effects in the body may result in inflammation, fibrosis, and permanent cirrhosis.

As stressed in this review, the fatty liver disease is not acquired by only one factor. Rather, it is a combination of genetic predisposition, resistance to insulin, oxidative stress, fatigue, lack of exercise, alcohol, and psychological stress, tobacco use, and other substances. These conditions often coexist with each other and compromise hepatic damage that enhances the speed of the disease advancement and the prevalence of chronic complications.

A key issue is that fatty liver disease is silent in its initial stages, therefore, making it hard to detect the disease at its initial stage until it has caused a lot of damage to the liver. The problem is that early identification provides a valuable chance of intervention, although dietary change, physical exercise, weight loss, abstinence of alcohol, management of stress, and smoking control are the most effective measures of prevention as well as control of this disease and have been based on lifestyle.

Finally, it is necessary to enhance the awareness of the interacting risk factors that are involved in alcoholic and non-alcoholic fatty liver disease to detect and prevent it. An interventional technique involving a combination of lifestyle change therapy and timely clinical treatment can go a long way in eliminating disease-progression and contribute to lessening the heavy burden of chronic liver disease.

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