REVIEW ARTICLE

Holistic Approach in the Management of Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD), in a few decades, is expected to be the commonest cause of end-stage liver disease and liver cancer surpassing all other etiologies. Urbanization and modern lifestyle have led to global epidemic of NAFLD with alarming prevalence rates across the globe. Its multisystemic involvement manifests as metabolic syndrome, diabetes, cardiovascular disease, end-stage liver disease, and hepatic and extrahepatic malignancies. The absence of promising therapy for halting disease progression in NAFLD is a challenge that is not only limited to liver disease but also other organs involved. It is unrealistic to expect any significant impact of pharmacotherapies in overall survival of NAFLD patients, given that the morbidity and mortality in these patients are contributed by conditions other than that of liver. Liver-centric approach in managing NAFLD will be futile unless the problem is dealt in a holistic manner. Lifestyle modifications have been repeatedly appraised in prevention and treatment of various diseases linked to metabolic syndrome including NAFLD. Despite being inexpensive and highly efficacious in prevention and treatment of different manifestations of NAFLD, lifestyle intervention often fails to gather sufficient interest among patients and physicians alike. This review intends to highlight pleiotropic nature of this disease, limitations of currently available pharmacotherapies and evidence that emphasizing lifestyle intervention is the only way to holistically deal in patients with NAFLD.

Keywords: Holistic approach, Lifestyle intervention, Multistysemic disease, Nonalcoholic fatty liver disease.

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Introduction

Nonalcoholic fatty liver disease is the most rapidly growing epidemic in the modern world.[1] The global incidence of NAFLD ranges from 28 per 1,000 person years to 52 per 1,000 person years subjected to geographical, ethnic, and gender variations.[2] The prevalence of NAFLD ranges from 13 to 30% and closely corroborates with daily energy available per capita.[3] Nonalcoholic fatty liver disease incorporates a spectrum of disease severity ranging from simple bland steatosis to nonalcoholic steatohepatitis (NASH) with or without fibrosis, decompensated liver disease, and liver cancer. Only a small proportion (4%) of NAFLD patients at any time will have advanced fibrosis.[3] Given the enormous burden of disease, these figures become largely inflated and NAFLD is now the most rapidly rising etiology for decompensated liver disease requiring liver transplantation and liver cancer.[4,5] In the next few decades, NAFLD is expected to surpass all of the other etiologies for liver diseases to become the leading cause of decompensated liver disease and liver cancer.

NAFLD: A Multisystemic Disease

Manifestations in NAFLD are not limited to the liver. It is now known to be a multisystemic disease with close ties with metabolic syndrome. While the diagnosis of NAFLD is a liver-centric one, the morbidities and mortalities associated with NAFLD are surprisingly led by cardiovascular diseases and extrahepatic cancers. Two pivotal epidemiological long-term studies have shown that liver-related deaths in NAFLD ranks in the third position; cardiovascular events and extrahepatic malignancies being the leading two causes.[6–8] Associations with chronic kidney disease, noncoronary cardiac abnormalities, diabetes mellitus, osteoporosis, and polycystic ovarian syndromes are other faces of NAFLD that contribute to impaired quality of life and overall morbidities in these patients.[9]

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Cardiovascular Outcomes in NAFLD

Insulin resistance and oxidative stress are the two fundamental pillars in the pathogenesis of NAFLD. Genetic, environmental, and dietary factors converge by different pathways resulting in these two events. Different components of metabolic syndrome which are also known to be risk factors for cardiovascular disease are highly prevalent in NAFLD.[10] A global systematic review and meta-analysis showed that among NAFLD subjects, 69% were dyslipidemia, 51% were obese, 40% were hypertensive, 40% had hypertriglyceridemia, and 22% were diabetic.[2] Moreover, 10 years risk of cardiovascular disease was found to be higher among NAFLD subjects than non-NAFLD controls when estimated by both atherosclerotic cardiovascular disease (ASCVD) pooled equation as well as Framingham risk score.[11] In a systematic review that included nearly 3,500 subjects, significant association between NAFLD and carotid intima media thickness (IMT) was observed.[12] Nonalcoholic fatty liver disease contributed to 13% increase in carotid IMT.[12] Similarly, coronary artery calcium (CAC) scores studied among nearly 10,000 subjects found NAFLD was associated with CAC score >0, metabolic syndrome, conventional cardiovascular risk factors, and existing cardiovascular disease.[13] Relationship between NAFLD

and structural vascular abnormalities is further supported by a meta-analysis based on 5,802,226 subjects with 99,663 CVD events that showed increased risk of fatal and nonfatal cardiovascular events among NAFLD patients as compared to controls HR 1.45, 95% CI (1.31–1.61). Further, also showed individuals with NASH with fibrosis had stronger association with these cardiovascular outcomes HR 2.5, 95% CI (1.68–3.72).[14]

Association between Malignancies and NAFLD

Malignancy remains the second commonest cause of mortality in subjects with NAFLD.[6,7] Long-term cohort study on 25,000 patients for 7.5 years found that there was an increase in overall cancer incidence rate in NAFLD subjects (782 per 100,000 patient years in NAFLD vs 582 per 100,000 patient years).[15] This was highest for hepatocellular carcinoma (HCC) [odds ratio (OR) 16.73], followed by colorectal cancer [OR 2.01] and breast cancer [OR 1.92]. High-NAFLD fibrosis score (NFS) and Fib 4 scores were associated with development of all cancers, including HCC. Another Longitudinal cohort study carried out among 4,700 obese and nonobese NAFLD patients with obesity-matched controls found that NAFLD patients were more likely to develop extrahepatic cancers irrespective of the presence of obesity.[16]

The impact of obesity alone on incidence of extrahepatic cancer was small. This study also explained that NAFLD may be the link between obesity and cancer association.[16] Another meta-analysis based on nearly 6,200 subjects also showed that NAFLD patients were also more likely to have colorectal adenomas OR 1.74, 95% CI (1.53–1.97).[17]

Hepatocellular carcinoma has been strongly associated with NAFLD. In a real-world European large cohort control study including 18 million subjects, NAFLD had higher risk of developing as compared to controls HR 3.51, 95% CI (1.72–7.16).[18] The link has been stronger in NAFLD with cirrhosis and warrants biannual HCC screening. This seems to be true for noncirrhotic NASH as well. A recent meta-analysis compared risk of HCC in noncirrhotic NASH with noncirrhotic liver diseases of other etiologies where they found increased risk of HCC in NASH-related liver disease, OR 2.61 95% CI (1.27–5.35).[19] The incidence of HCC in noncirrhotic NASH is not yet clear and varies between 2.4% over 7 years and 12.8% over 3 years.[20] Biannual screening for HCC in noncirrhotic NASH is not recommended at the moment.

Caveats of Currently Available Pharmacotherapy

Pharmacological therapies for NAFLD are rapidly evolving. A number of novel molecules are under investigations but only a very few have shown promise in improving fibrosis, resolution of inflammation and NASH, and decreasing steatosis. Currently, limited drugs, including vitamin E and pioglitazone, have been approved for histologically proven NASH but they have failed to show unequivocal evidence in resolution of fibrosis.[21–23]

Nonalcoholic fatty liver disease is a multifactorial disease with genetic and environmental components that include diet, activity, and lifestyle. There is growing evidence that trends in the prevalence of NAFLD follow modern and urban lifestyles, including evolving food cultures. It is understandable that for a disease with such huge burden, close association with lifestyle and dietary pattern, and multisystemic involvement, currently available pharmacological therapies are unlikely to make an impact in reduction in mortality and morbidities. Further, the role of pharmacotherapy in prevention of cardiovascular mortality and cancer, the two main causes of death in these patients, remains to be addressed. Therefore, liver-centric approach in the management of NAFLD is inadequate and a holistic approach addressing different facets of this syndrome needs to be emphasized.

Evaluation of NAFLD with Holistic Perspective

Cardiovascular Evaluation for NAFLD

Cardiovascular disease is the leading cause of death in NAFLD and it has close association with metabolic syndrome. It is therefore mandatory to assess metabolic and cardiovascular risk factors in NAFLD subjects. Routine screening with echocardiography, treadmill testing, or electron-beam computed tomography is not recommended by the US Preventive Services Task Force for low congenital heart disease (CHD) risk in general population.[24] In absence of guidance for CVD screening in noncirrhotic NAFLD patients, the same recommendation should apply. To identify high-risk patients, who should proceed for further screening testing, traditional cardiovascular risk factors can be used. Diabetic and obese subjects with body mass index (BMI) >35 kg/m^2 are at high risk and even presence of one other risk factor stratifies them into high-risk categories. Those with high risk and listed for transplant should be evaluated further.[22] Among others, pooled equation to calculate ASCVD risk score or Framingham risk score to estimate 10 years CVD risk is helpful for calculating 10 years cardiovascular risk. Estimated 10 years risk for cardiovascular event exceeding 10% should be subjected to further cardiovascular evaluation. Dobutamine stress echo and CAC score can be noninvasive screening tools.[25] Conventional angiography is the gold standard for diagnosis and assessment of coronary artery lesion and therapeutic interventions can be done.[25] Considerations should be made for initiation of statin and aspirin when appropriate.[26] Optimization of lipids and appropriate counseling for lifestyle modification and management of obesity are common denominator that should be applied when appropriate to all NAFLD patients.

Extrahepatic Cancer Screening for NAFLD

While strong links have been found among NAFLD and gastrointestinal (GI) cancers, breast cancer, and gynecological cancers, there is still paucity of data on as to when and how to screen NAFLD population. In a recent meta-analysis, strongest link has been found with colorectal cancer with 1.5–2 times increased risk followed by other breast cancer, GI cancer, and gynecological cancers where the risk is about 1.5 times.[27] These risks were independent of obesity. Cost-effectiveness of colorectal cancer screening among NAFLD with family history of colorectal cancer was studied using fecal immunological test, flexible sigmoidoscopy, and colonoscopy. Though colonoscopy starting at the age of 40 years was found to be effective in decreasing colorectal cancers, initiation of colonoscopy at the age of 50 years and repeating every 10 years was found to be a cost-effective strategy.[28] Until availability of solid data on effectiveness of extrahepatic cancer screening, any recommendations cannot be made.

Evaluation of Liver Disease

Abnormal liver function tests are the commonest abnormality and often the initial findings that lead to the diagnosis of NAFLD.[29] The main motive of evaluation lies in the detection of steatohepatitis and fibrosis. A few biomarkers have shown to be promising in the

detection of NASH. Cytokeratin 18 (CK 18) and the terminal peptide of procollagen III (PIIINP) have shown reasonable accuracy but need further validation.[30,31] As of now, liver biopsy remains the only effective way of diagnosing NASH. Fibrosis is a surrogate for disease progression and selecting patients for liver biopsy and/or treatment. Fibrosis not only predicts liver-related outcomes, but there is accumulating body evidence that fibrosis closely relates to cardiovascular outcomes and risk of extrahepatic malignancies.[14,16] Therefore, the assessment of fibrosis has become pivotal to initiate treatment, determine aggressiveness of therapy, as well as prognosticate patients with NAFLD.

Validated noninvasive tools for assessment of fibrosis include BARD score, Fib4, APRI, and NAFLD fibrosis score.[32–34] Transient elastography and ultrasound-based elastography [Shear wave elastography, acoustic radiation force impulse (ARFI)] are available to measure liver stiffness.[35–37] Combination of noninvasive scores and measurement of liver stiffness have been shown to be useful in ruling out significant liver fibrosis and selecting those who should be biopsied.[38] Liver biopsy remains the gold standard in diagnosis of NASH as well as fibrosis staging that helps in prognosticating the patients and to determine how aggressive the therapeutic interventions should be.

The major limiting factor in the pharmacological treatment of NASH is the lack of effective molecules. So far, vitamin E and pioglitazone are the only two drugs that have been approved for the treatment of NASH and both drugs have not shown any promising results in regression of fibrosis or improvement in overall survival.[21–23] Other molecules in pipelines, including obeticholic acid, have shown promise in resolution of NASH and even regression of fibrosis but are yet to be approved widely.[39]

Holistic Management of Patients with NAFLD

Nonalcoholic fatty liver disease is associated with impaired quality of life and significant economic burden apart from hepatic and extrahepatic morbidities and increased risk of mortality.[40–42] The goal of management of NAFLD should be to improve quality of life and overall survival and should address all risk factors to achieve the same. While primary prevention of coronary artery disease and atherosclerotic disease is well established, it is not yet clear if long-term interventions can prevent liver cirrhosis and extrahepatic malignancies. The lack of reliable surrogate in predicting adverse outcomes in NAFLD is lacking. So far, only liver fibrosis has been shown to predict liver-related outcomes.[43] Though there is accumulating evidence that fibrosis may be related to cardiovascular outcomes and increased incidence of extrahepatic malignancies, data are not that robust.[7,14,15]

Pharmacological therapy has its inherent limitations given the wide array of multisystemic manifestations of NAFLD. Drugs that target steatohepatitis and fibrosis are unlikely to address these multisystemic issues. Therefore, a multifaceted approach needs to be emphasized in the management of NAFLD rather than being centered toward the liver. Use of aspirin, statins, and coronary interventions should be considered when appropriate. Pharmacotherapy for NASH should be initiated with currently approved therapies if there is evidence of NASH and/or significant fibrosis.

Lifestyle Intervention: Diet, Exercise, and Weight Loss

Lifestyle intervention leading to weight loss in subjects with NAFLD is perhaps the most efficient intervention that can have a global impact on overall survival.[44] Proper interventions with either dietary modification or exercise can improve steatosis (hepatic triglyceride content) and help in NASH resolution. But achieving weight loss was crucial for improvement in fibrosis. In a randomized control trial involving 293 histologically proven NASH, lifestyle intervention leading to weight loss more than 7% from baseline alone has shown to reduce steatosis by 76%, steatohepatitis by 64%, and fibrosis by 50%; weight loss >10% led to reduction of steatosis by 100%, steatohepatitis by 90%, and fibrosis by 81%.[45] This degree of improvement in histology including fibrosis has never been achieved by pharmacotherapy. Further, its impact on prevention of coronary and atherosclerotic vascular disease cannot be overemphasized. However, only 19% of the subjects who undergo lifestyle intervention were able to achieve >7% weight loss.[45] After lifestyle intervention, maximum weight loss was noted in the first six months and there was tendency for weight gain over long-term follow-up.[46,47] Regain of weight >1.5 kg and lack of exercise were associated with recurrence of NAFLD,[48] but, despite regain of weight, favorable effect on hepatic steatosis, insulin resistance, and HbA1C persisted.[49,50]

Achieving weight loss is difficult, many patients lack confidence, require determination, and are often difficult to maintain.[51]

Dietary Interventions in NAFLD

Dietary intervention alone has shown to improve liver fat content and steatohepatitis. Combination of dietary intervention and exercise is an effective way of losing weight and hence it is an integral part of management in NAFLD. Dietary interventions can be done in several ways. These include modifying calorie content, altering macronutrients, or modifying eating patterns.

Modifying Calorie Content

Calorie reduction is one of the most conventional and widely accepted ways of dietary approach. Shifting calorie balance to the negative side can help reduce liver fat content, improve steatohepatitis, and achieve weight loss. Reduction of calorie content to achieve 500–1000 kcal deficit is found to be effective and recommended widely.[23,52] It can be done by cutting down simple carbohydrates and replacing them with complex carbohydrates and fibers. Extreme forms of calorie restriction to up to <800 kcal/day have been studied for short-term interventions. These include low-carbohydrate diet (LCD) where carbohydrate intake is restricted to <130 gm/day and energy intake of <800 kcal and very low-calorie diet (VLCD) with total calorie restricted to <800 kcal/day[53–55] and carbohydrate content 20–50 gm/day.[56,57] The results of these interventions were found to be effective in reduction of hepatic fat content, weight loss, and improving liver biochemistry. Despite being effective in weight reduction and beneficial in terms of reducing liver fat, low-calorie diet is difficult to maintain and rebound to initial weight has been seen in experimental studies.[46–50] Reduction of calorie intake has been associated with reduction in basal metabolic rate and total energy expenditure which may plateau the effect of calorie restriction over several months.[58] Recently, long-term follow-up data from NHANES between 1999 and 2010 raised concern of higher all-cause mortality rate among subjects on LCD.[59] Another report based on NHANES survey

between 1999 and 2014 analyzed quality of diet. It was evident from that unhealthy low-carbohydrate diet was associated with high all-cause mortality while healthy LCD were beneficial.[60]

Modifying Macronutrient Composition

Several approaches have been used to alter macronutrients in order to reduce liver fat content and even weight loss. These approaches include iso-, hypo-, or hypercaloric diets but with varying proportions of fat and carbohydrates. Quality of fats can also be altered by replacing saturated fats with poly- and monounsaturated fats.

Low-carbohydrate High-fat Ketogenic Diet

Ketogenesis has been shown to have a significant role in reducing liver fat, weight reduction, and improvement in histology including fibrosis. Benefits of ketogenesis in NAFLD and metabolic syndrome have been proposed to be beyond weight loss. Modulation of gut microbiome and increased folate production has been elegantly shown with experiments inducing ketosis.[61] Recently it has been proposed that ketone bodies are capable of epigenetic modifications of key histones that in-turn serve as regulators of chromatin architecture and gene transcription.[62]

By altering gene transcription and modifying gut microbiome, ketones can potentially have roles in mitigating inflammatory pathways in NAFLD.

Very low-carbohydrate intake <20–50 g/day is required to induce ketosis. Ketogenic diet can be slightly hypercaloric, isocaloric, or hypocaloric. Two basic types of ketosis have been studied: high-fat ketogenic diet (HFKD) with unrestricted fat intake and very low-calorie ketogenic diet (VLCKD). High-fat ketogenic diet includes carbohydrate content of <20–50 g/day and no calorie restriction. While VLCKD contains carbohydrates of <20–50 and calories restricted to <800 kcal/day. High-fat ketogenic diet shows reduction in weight, improvement in liver biochemistry, and reduction of hepatic fat content and histology.[63–65] When compared to low-fat high-carbohydrate hypocaloric diet, weight loss and reduction in intrahepatic triglyceride content were similar to HFKD. Studies on VLCKD, however, have shown conflicting results. In these studies, weight loss was consistently observed.[66,67] Some studies also showed improvement in hepatic fat content.[66,68,69] But in a few, they failed to show improvement in transaminase levels.[66–68] It needs to emphasize that most of these studies are short-term, constitute a small number of subjects, and have marked heterogeneity in between studies. Ketogenic diet is likely to be helpful as a short-term intervention to rapidly induce weight loss and hepatic fat reduction. However, the safety of ketogenic diet remains questionable especially in subjects with comorbidity, diabetes, and pregnancy. Further, adherence to a VLCKD remains another concern.

Quality of fat has been seen as an important determinant of hepatic steatosis. Isocaloric and hypercaloric diets containing high saturated fat content and low polyunsaturated fatty acid (PUFA) and monounsaturated fatty acid (MUFA) were seen to increase liver fat, while isocaloric diets rich in MUFA and PUFA were seen to reduce hepatic fat content.[70]

Mediterranean Diet

Mediterranean diet (MD) is considered to be the healthiest diet and has shown multiple benefits including reduction of cardiovascular risk, lipid profile, HbA1C levels, weight loss, and improvement in liver fat content.[71–73] It is considered to be a plant-based diet and characterized by a high ratio of MUFA to saturated fatty acids (SFA). Mediterranean diet is rich in fat, accounting for 30–40% of daily energy consumption and abundant in fibers, whole grains, legumes, fish, and seafood. Meat and dairy products are consumed in a lower proportion. Monounsaturated fatty acid and PUFA are associated with improvement in liver fat, insulin resistance, and subsequent reduction of cardiovascular risks.[71] Fibers help in modulation of gut microbiome and increased production of phenols and short-chain fatty acids that are known to have antioxidant properties.[74] Adherence seems to be better with MD and was helpful in long-term maintenance.[23]

Altering Eating Pattern

Studies on eating patterns have shown that modern lifestyle constitutes an eating period of nearly 18 hours.[75] Fasting has shown to be an effective way of altering metabolism that helps in improving steatosis, liver function, and even weight loss.[76] It helps to decrease insulin resistance and improve autophagy. During the first four days of fasting, decreases in insulin and glucose levels were noted with increase in oxygen consumption, resting energy expenditure, and ketone levels.[77]

There are several types of intermittent fasting methods. Alternate days fasting (ADF) includes fasting days of zero-calorie intake followed the next day by unrestricted calorie intake. While modified ADF constitutes 20–25% calorie intake during fasting days. Time-restricted fasting alters the eating pattern by allowing eating time to 8 hours a day and fasting period of rest of 16 hours.

Alternate days fasting has shown to decrease body weight, fat mass, improve lipid profile, increase PUFA and ketone bodies, and decrease T3 levels.[76] Among healthy nonobese nondiabetic subjects, ADF was seen to be safe to practice for several months. Recent meta-analysis on intermittent fasting that included six studies showed beneficial effects on reduction of weight, BMI, and liver enzymes. However, it failed to show any improvement in lipid profile and liver stiffness.[78] Heterogeneity among studies in terms of method of fasting used, small number of subjects in the studies and short period of interventions were limiting factors in this meta-analysis.

Sedentary Life, Physical Activity, Exercise

Though these terms seem analogous, sedentary life, physical activity, and exercise are different. Sedentary behavior means "any waking activity characterized by low level of energy expenditure (<1.5 metabolic equivalents of tasks or METS) and sitting or reclining posture".[79] Multiple studies have found the association of sedentary period with metabolic syndrome and liver fat.[80,81] Not only the total duration of the sedentary period but how it is broken also seems to be important.[82] Thus, reducing the total sedentary time as well as taking frequent breaks might be helpful in patients with NAFLD.

Physical activity refers to any activity done while not at rest. The level of physical activity correlates with the prevalence as well as the severity of NAFLD. The general guideline of walking 10,000 steps a day or 150 minutes of moderate physical activity in a week for prevention of CVD appears plausible for NAFLD as well.[83,84] Self-monitoring of the daily step count via pedometers or mobile apps may be useful to ensure the recommended daily physical activity.

Exercise

Exercise refers to "planned, structured, and repetitive movement performed to maintain or improve fitness".[85] Its benefits are established beyond reduction in liver fat. This is important as

cardiovascular risk reduction is an important aspect of NAFLD care. Recent studies have shown that both aerobic and resistance exercise are equally beneficial in terms of reducing liver fat content.[86] Intensity and energy expenditure were more with aerobic exercise but required cardiorespiratory fitness as compared to resistance exercise.[86] While higher intensity exercise is more efficient in reduction of cardiovascular risk, it is unclear whether moderate-intensity or vigorous-intensity exercise is better for liver fat.[87,88] The intensity of exercise is further determined by baseline cardiorespiratory fitness, underlying comorbid condition, and availability of time. Moderate-intensity exercise of 3.5–5.9 MET for 150 minutes per week has been recommended by different guidelines.[23] However, high-intensity vigorous exercise of >6 MET for 75 minutes per week was seen to be better in terms of reducing cardiovascular risk.[89] High-intensity intermittent training (HIIT) uses vigorous activity with intervals of recovery time. High-intensity intermittent training was found to be as good as moderate-intensity exercise in reducing liver fat as well as cardiovascular risk and seems suitable for individuals where availability of time is a concern.[90]

Resistance exercise is another form of exercise where muscles are used against a load. It has a beneficial effect in reducing liver fat content and weight loss.[91] After resistance training, the metabolic activity is increased by 20% up to 48 hours and results in additional calorie loss after exercise.[92] It is suitable for individuals with comorbidities, such as osteoarthritis, and lower level of cardiorespiratory fitness.[86] Precise exercise prescription in NAFLD is lacking as there is no clear understanding on the type and intensity of exercise that gives the best results. Frequency, intensity time, and type of exercise should be determined by individuals' cardiorespiratory fitness level, time availability, underlying comorbid condition, and feasibility to keep it sustained.

Barriers in Implementing Lifestyle Modification and Coping Strategies to Overcome Them

One of the biggest barriers in lifestyle modification is adequate motivation to sustain healthy behavioral changes. There are different facets of this problem which include lack of proper information regarding the disease, potential benefits of lifestyle intervention, adequate information on how to adopt these behavior changes, information regarding healthy dietary options, and choosing proper exercise techniques. A good counseling and adequate information is the key to motivate and make patients realize the potential benefits of lifestyle interventions. Setting specific, measurable, achievable, relevant, and timely (SMART) targets, formulating action plans, recognizing potential barriers for adopting lifestyle changes, and coping strategies for the barriers may help in initiating and maintaining these behavioral changes.[93]

Conclusion

Nonalcoholic fatty liver disease is a multifaceted disease with multisystemic involvement. Currently, research on NAFLD has been predominantly focusing on pharmacotherapies to improve liver-related outcomes. The end points set in these therapeutic trials are either histological changes or improvement in liver fat content and transaminase levels. A very few of them have shown unequivocal evidence of fibrosis regression and none has addressed long-term outcomes in terms of overall mortality, including cardiovascular complications and occurrence of malignancies. It is therefore very important to realize that treating these patients requires a holistic perspective so as to reduce risks of multisystemic complications and overall mortality. While doing so, currently available evidence shows weight reduction and lifestyle modification as the only way to improve overall metabolic risk factors.

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