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Review Article

Role of diet and lifestyle modification in the management of nonalcoholic fatty liver disease and type 2 diabetes

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is considered as the hepatic evidence of insulin resistance which is the hallmark of type 2 diabetes. NAFLD is considered as the risk factor for developing type 2 diabetes and has a high frequency of occurrence in those with existing type 2 diabetes. Compared with patients with only NAFLD or type 2 diabetes, these patients show a poor metabolic profile and increase mortality. Hence, effective treatment strategies are necessary. Here, we review the role of diet and lifestyle modification in the management of NAFLD and type 2 diabetes. Based on the available studies, it has been shown that the addition of any kind of physical activity or exercise is beneficial for patients with both NAFLD and type 2 diabetes. Proper dietary management leads to weight loss are also effective in improving metabolic parameters in patients with both NAFLD and type 2 diabetes. In conclusion, it is clear that increasing physical activity or exercise is effective in improving metabolic parameters in patients who are suffering with both NAFLD and type 2 diabetes.

Keywords: *Hepatic steatosis, Insulin resistant, Nonalcoholic fatty liver disease, Physical activity, Type 2 diabetes*

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is now considered as one of the most common liver disorders and its prevalence expecting to increase further in the near future [1]. NAFLD constitutes a spectrum of pathological conditions such as nonalcoholic steatohepatitis (NASH), hepatic steatosis, hepatocellular carcinoma (HCC), terminal liver failure, cell necrosis, perilobular, and cirrhosis [2]. The continuously increasing frequency of obesity in today's generation is linked with many health issues including NAFLD [3,4]. These include diabetes, hyperlipidemia, hypertension, cardiovascular, and fatty liver diseases. These set of conditions exhibit metabolic syndrome [5]. NAFLD is a complex disease that includes the interaction of genetics, diet, and lifestyle. About 50% of patients who are suffering with type 2 diabetes have NAFLD. The interconnection between type 2 diabetes and NAFLD is recently recognized and less well known to physicians. Because patients are usually asymptomatic and routine blood test are usually normal, it may be a diagnosis that is overlooked in type 2 diabetic patients [1,6].

Patients with NAFLD who have type 2 diabetes are particularly at risk of progressive forms of the disease and that they are at higher risk of developing cirrhosis contrast to those who do not have diabetes [7,8]. Although cardiovascular disease is the major cause of excess morbidity and mortality in type 2 diabetes, liver failure may also be considered to be a threat to patients who are suffering with type 2 diabetes NAFLD [8,9]. As NAFLD and type 2 diabetes are associated with obesity, weight loss constitutes the principle key in NAFLD management. Sudden weight loss achieved through dietary and lifestyle modification may lead to the progression of liver failure in some NAFLD patients. Alternatively, weight loss using surgical methods, even with rapid weight reduction after surgery, has been successful in reducing NAFLD progression [10-12]. This review highlights the role of diet and lifestyle modification in the management of NAFLD and type 2 diabetes and also focuses on human studies related to physical activity and dietary modifications.

Diet management in nonalcoholic fatty liver disease and type 2 diabetes

The central features of NAFLD pathogenesis comprise metabolic dysregulation (increased steatosis, mitochondrial

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dysfunction, and insulin resistance), inflammation, apoptosis, and fibrosis. Carbohydrates, fatty acids, proteins, amino acids, and Vitamin D can simultaneously either activate or inhibit the critical nodes of NAFLD pathogenesis. Figure 1 shows mechanisms involved in parthenogenesis of NAFLD and its possible treatment options.

Carbohydrates

Normally, human diet is naturally rich in carbohydrates [13] and some epidemiological studies have shown a strong relationship between increase in fructose intake and occurrence of NAFLD [14]. Low-level carbohydrate diet <45% per day has shown positive results regarding depletion of intrahepatic triglyceride content, weight loss, and development of metabolic parameters in obese patients. When the consumption of fructose exceeds 25% of the energy requirement, it will show the effects on glucose homeostasis, free fatty acid metabolism, etc. [15]. Fructose slows down the hepatic lipid oxidation by blocking the action of peroxisome proliferator-activated receptor alpha [16] and increases fibroblast growth factor 21 (FGF21) in a CHO-response element-binding protein-dependent manner even when protein consumption is controlled [17].

Fructose-driven biochemical alterations lead to steatosis, obesity, insulin resistance, hepatic fibrosis, inflammation, etc. [16,18,19]. In contrast, a carbohydrate such as resistant starch that is resistant to digestion, which is found in many food materials, it can helps to maintain the blood glucose levels. Therefore, It can decreases the risk of the type 2 diabetes [20,21]. Gut flora which include Bactericides, Bifidobacterium, etc., are responsible for metabolizing fermentable polysaccharides such as pectin or insulin to produce short-chain fatty acids, which not only improve insulin resistance [22] but also activate G protein-coupled receptors to induce epigenetic and anti-inflammatory effects to modulate metabolic disease status [23,24].

Some studies have shown beneficial results of dietary fibers on body composition parameters such as reduced body fat percentage, insulin resistance, and waist circumference. Dietary fibers are composed of plus lignin, nonstarch polysaccharides, resistant starch, and oligosaccharides. These fibers present in food containing hemicellulose, cellulose, hydrocolloids, resistant starch, and resistant oligosaccharides. And also, the fibers are classified into two types: soluble and insoluble dietary fibers. Insoluble dietary fibers are insoluble in gastric fluids and water; whereas, soluble dietary fibers are soluble in water and can withstand GI enzymatic digestion. Soluble fiber passes through small intestinal and reaches the colon where the soluble fiber can be fermented by intestinal microflora (Bactericides, Bifidobacterium, etc.) [25]. Both insoluble and soluble fibers play different roles in maintaining gastrointestinal health [26]. Information regarding the effect of different kinds of fiber remains unclear [27]. Thus, current research is permitted to determine the optimal requirement of dietary fibers for prevention and reduction of NAFLD and type 2 diabetes.

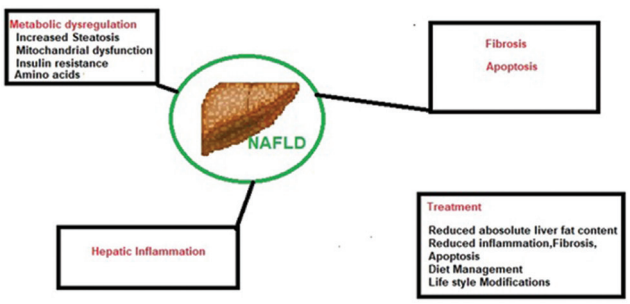

Figure 1: Pathogenesis and treatment of nonalcoholic fatty liver disease

Fatty acids

Dietary fatty acids can regulate the action of key cell types such as macrophages and hepatocytes implicated across the NAFLD spectrum [28]. Dietary fatty acids can easier the development, reversal of some NAFLD features depending on fatty acids' composition, the molecular targets they hold, carbon chain length, etc. [29,30]. Over-injection of saturated fatty acids promotes fatty liver, induces hepatic endoplasmic reticulum stress, and impairs insulin signaling and apoptosis [28-33]. Saturated fatty acids induced oxidative stress which results in the activation of the c-Jun N-terminal kinase (JNK) pathway, which acts as a key mechanism in the pathophysiology of NASH and insulin resistance [34].

In some studies, it has been shown that monounsaturated and polyunsaturated fatty acids such as oleic acid, arachidonic acid, alpha-linolenic acid were found in dietary foods like avocados, olive oil and nuts. They can reduce intrahepatic triglyceride accumulation and inflammation. Examples: Dietary intake of polyunsaturated fatty acids in a cross-sectional study of patients with NAFLD showed that >80% of patients did not reach daily recommended intake of linolenic acids and linolenic [35]. Well-controlled human clinical trials have shown that n-6 polyunsaturated fatty acids (linoleic acid) compared to saturated fatty acid (butter) prevent intrahepatic triglyceride in the context of 7 weeks of overfeeding [36].

NASH patients had a significantly higher n-6 fatty acids and a decrease ratio of n-6/n-3 fatty acids [37]. Treatment with glucagon-like peptide-7 analog improves steatohepatitis and modulates the hepatic n-3/n-6 ratio by the regulation of hepatic fatty acid metabolism [38]. Both quantity and quality of dietary fat may alter the glucose tolerance and insulin sensitivity [39-41]. The presence of high-fat content in the diet may cause a decline of glucose tolerance by several ways which include reduced binding of insulin to its receptors decreased quantity of glycogen synthase, impaired glucose transport, and aggregation of stored triglycerides in skeletal muscle [42-46].

In animal experiments, saturated, monounsaturated, and polyunsaturated fatty acids have produced insulin resistance when given as high-fat diets [45-49]. According to epidemiological studies, higher intake of saturated fat results in increased risk of impaired glucose tolerance and increased fasting glucose and insulin levels [50,51]. High content of saturated fatty acids in muscles phospholipids or serum lipids

is connected with increased fasting insulin levels, reduced insulin sensitivity, and greater chance of developing type 2 diabetes. Whereas, higher intake of vegetable fat (unsaturated fat) is associated with lower risk of developing type 2 diabetes [52,53]. High content of long-chain polyunsaturated fatty acids in skeleton muscle phospholipids leads to increased insulin sensitivity in human [54,55]. The epidemiological data are in consistent regarding monounsaturated fatty acids. Some studies have shown that higher consumption of monounsaturated fatty acids may be harmful regarding increased diabetes risk [56,57]. Adequate amount of fatty acids <30% is necessary to show its beneficial effects in NAFLD and type 2 diabetes patients.

Proteins and amino acids

Liver fat levels can be reduced by high-protein diet. Increasing dietary protein content reduces the level of triglyceride diffusion in the liver [58]. Adequate amount of proteins, 15%–20%, is necessary to show its beneficial effects in NAFLD and type 2 diabetes patients. A prospective study of 37 patients with type-2 diabetes and NAFLD fed a high-protein diet showed a 36% to 48% reduction in intrahepatic triglyceride levels, regardless of even if the protein came from plant or animal source [59].

In a subset of PREVIEW (Prevention of Diabetes through Lifestyle Intervention and Population Studies in around the world) cohort, 25 patients with NAFLD who were insulin resistant and obese were administered a weight maintaining protein diet containing either 15% or 25% protein for up to 2 years following an initial reduction in weight for a period of 8 weeks. In both groups, visceral adipose tissue levels, intrahepatic triglyceride levels, homeostatic model assessment score for insulin resistance, subcutaneous adipose tissue levels, and insulin sensitivity were reduced independent of body weight [60]. A recent trial combining moderate carbohydrate restriction (30% of calories) with a high-protein diet (30%) decreased the absolute hepatic fat content by 2.4% in adults with type 2 diabetes in contrast to 0.2% increase observed in those on a high carbohydrate (50%) and normal protein diet (17%) [61,62]. Neither protein nor leucine ingestion altered plasma adiponectin or nonesterified fatty acids concentrations. Therefore, 3-hydroxyisobutyrate (HIB) and fibroblast growth factor 21(FGF21) might be involved in protein-mediated insulin resistance [63].

Further, preclinical studies suggest that high-protein diet may have negative impacts on insulin sensitivity, whereas low-protein diet shows metabolic benefits [64-69]. Adequate amount of protein consumption (10%–15%) is beneficial and shows positive results regarding weight loss in patients with NAFLD and type 2 diabetes [70]. These studies show the importance of balancing the quantity and quality of dietary protein relative to other nutrients as a key element of metabolic health. Certain amino acids in the diet may preferentially regulate key biological processes. Recent studies reported that when specific dietary amino acids are matched to protein coding genes, growth and reproduction are enhanced without affecting the life span [71].

In some studies, It has been shown that amino acids may regulate certain aspects of NAFLD pathogenesis such as fibroinflammation and glucose homeostasis. Oral supplementation of amino acids in type 2 diabetic patients which can results in decreasing of postprandal plasma glucose levels without any change in insulin levels in plasma. Animal proteins consist of high amount of homocysteine, cysteine, and methionine on metabolism; they give a rise to sulfate (transsulfuration), which is considered as an important requirement of the daily acid load. The metabolism of these amino acids occurs in the liver, which is known as one carbon metabolism. Accumulation of these amino acids takes place due to dysregulation of the above pathway in the plasma and liver, which acts as a risk factor for NAFLD, facture, and cerebrovascular disease [72-74].

Plant proteins consist of high amount of glycine and glutamate that requires high proportion of H_2 ions to be metabolized alkalinizing the microenvironment [75,76]. Compared to vegetarian diet, animal protein-based diets consist of the high amount of ornithine and glutamine, which is considered as major precursors for ammoniagenesis [77]. An increase in dietary vegetable protein improves the blood glucose response in persons with type 2 diabetes [78]. One more study has shown that depletion of alanine aminotransferase after high-level protein diet was provided to the NAFLD patients [79]. An increase in renal plasma flow and glomerular filtration rate is associated with consumption of high animal protein diet, which is not seen in case of vegetable protein diet [80,81].

One more study demonstrated that a vegetable diet with low amounts of methionine and aromatic amino acids, but rich in branched chain amino acids (valine, leucine, and isoleucine), helped to improve the health condition of patients suffering with cirrhosis associated with mild portal-systemic encephalopathy [82]. Branched chained amino acids also stimulate insulin production and glucose uptake from stem cells and liver [83]. When branched chain amino acids are supplied to men who are suffering with obese cirrhosis, It can resultant to decrease in the development of HCC and also upgrades the survival rate leads to decrease in the development of HCC and upgrades the survival rate [84,85].

Low plasma content of branched chain amino acids and glycine in NAFLD and type 2 diabetes patients is inversely connected with insulin resistance. Epidemiological studies show that high-protein consumption for short term does not interfere with calcium homeostasis, but on the long term, it reduces the incidence of bone fracture [86]. High amount of amino acids in the diet promotes increased glomerular filtration rate, serum uric acid, albuminuria, and urinary pH value, which promotes chronic kidney disease progression. Consumption of a high-level protein diet obtained from dairy products contains high amount of proline and glutamic acid and has been connected with high chances to develop diabetes. High consumption of branched chain amino acids with high-fat diet leads to aggregation of succinyl and propionyl-CoA, which might interfere with the tricarboxylic acid cycle, glycolysis, and insulin sensitivity through mitochondrial stress.

Recent evidences have shown that amino acids can cause inhibition of insulin signaling through a mechanistic target of rapamycin activation [87,88]. Effects caused due to high-protein diet in NAFLD patients remain controversial. Therefore, more intense randomized clinical trials are necessary where the effect of single amino acid pool subscription over health must be explored.

Vitamin D

Vitamin D is considered as a fat-soluble hormone which is acquired from sunlight exposure and dietary supplements. Oily fish and fortified food are dietary supplements which includes cereals, soya milk and shiitake mushrooms. Sunlight is a major source of Vitamin D up to 90%. 7-dehydrocholesterol in the skin gets converted to form pre-Vitamin-D_3 upon sunlight exposure (UVB irradiance), which is later converted to Vitamin D_3. The term Vitamin D includes ergocalciferol or Vitamin D_2 or cholecalciferol or Vitamin D_3. The principal metabolites of Vitamin D are calcieliol (25(OH)D) or 25-hydroxy Vitamin D and calcitriol (1,25-(-$OH)_2D_3$) OR 1,25-dihydroxy Vitamin D_3, which vary in their hydroxylation patterns. In humans, skin is the main source of Vitamin D obtained through the cutaneous synthesis of Vitamin D_3 or cholecalciferol and small amount is obtained through the intake of food which are rich in Vitamin D_2 or Vitamin D_3.

Circulating Vitamin D gets bound to the Vitamin D-binding protein, through which Vitamin D is transported to the liver, their Vitamin D 25-hydroxylase changes it to 25(OH)D, where 25(OH)D is converted to 1, 25-(OH)D in the kidney which is the most biologically active form. 25-hydroxy Vitamin D-1 alpha-hydroxylase (CYP27B1) is the enzyme which is responsible for the above transformation. The presence of Vitamin D receptors demonstrates that Vitamin D also plays a major role beyond bone metabolism. Recently, two quantitative meta-analyses concluded that the amount of 25(OH)D was low in patients with NAFLD compared to those people without fatty liver [89,90]. In cross-sectional studies only, limited evidence is provided against the effectiveness of Vitamin D supply in patients who are suffering with NAFLD [91,92].

From animal model, information is provided that Vitamin D interferes with the activation of perisinusoidal cells (also known as hepatic stellate cells [HSCs]) and plays an important role in collagen deposits and extracellular matrix remodeling leads to fibrosis (fibrotic scarring) [93]. Vitamin D inhibits proliferation of HSC; clinical trials are required to reveal that Vitamin D supplementation might reduce the advancement from NAFLD to NASH. Vitamin D also plays an important role in bone homeostasis [94].

Insufficient levels of Vitamin D have been found in patients with osteoporosis, even though the only moderate amount of favorable effects of Vitamin D supplementation has been reported in facture prevention [95]. In last few years, mounting curiosity has been conveyed to Vitamin D action on skeleton muscle. Decrease in Vitamin D levels has been linked with disability, falls in the elderly and sarcopenia. Vitamin D deficiency in adults shows histological changes in muscle fiber composition and width [96]. Serum Vitamin D levels increased through weight loss and enhanced the metabolic parameters in patients with NAFLD [97].

In this study, it has been found that compared to Vitamin D deficiency supplement weight loss was more effective in increasing serum Vitamin D level in patients with NAFLD. In addition to potential effects of Vitamin D on immune and inflammation processes, other studies are also necessary to look over whether Vitamin D decreases oxidation stress in patients with NAFLD. Some animal studies show that Vitamin D has some beneficial effects, in which one of the studies states that Vitamin D decreases tumor necrosis factor alpha. At the present times, exact convincing data are not there to support that the use of Vitamin D to enhance the results in NAFLD. However, people who are suffering with Vitamin D deficiency should be medicated and given proper musculoskeletal benefits.

Vitamin D controls insulin secretion by regulating voltage gated calcium channels. Calcitriol plays an important role as a chemical messenger by interacting with various receptors, which are regulating calcium flux in B-lymphocytes (beta cells). B-lymphocytes are situated on the phospholipid layers of the plasma membrane.

In case of Vitamin D deficiency normal insulin secretion may be altered through changes in flux in B-lymphocytes. Therefore, appropriate insulin secretion by pancreatic beta cells is essential [98,99]. Preclinical studies demonstrate that Vitamin D can decrease the excitability of the renin angiotensin system and therefore, enhances the function of B-lymphocytes [100]. An adequate amount of Vitamin D level may also enhance insulin resistance pathways connected with diabetes. It is mainly caused due to changes in calcium flux and concentration along the cell membrane of insulin-responsive tissue [101].

Regulation of intracellular and extracellular calcium concentration stimulates dephosphorylation of glucose transporter-4 operates a decreased insulin-stimulated glucose transport [102]. 1, 25-(OH)2 D accelerates the expression of insulin receptors and thus, accelerates insulin sensitivity. Calcitriol proliferator-activated delta receptor (PPAR-d) is a transcription factor which is responsible for regulating the fatty acid metabolism in skeleton muscle and adipose tissue. Insulin resistance also gets decreased by the specific actions of a calcitriol on hepatic lipid synthesis, glucose output, and on skeleton muscle [100].

Calcitriol plays an important role in a wide range of metabolic pathways by binding to the VRD and dimension of its substrate 25(OH)D is the principal marker for health issues. The receptor is present in various cells of Langerhans pancreatic B-lymphocytes, adipose, muscle, and liver [103,104]. Fat tissue is the main storage place for Vitamin D. High body mass index is linked to reduce Vitamin D concentration. Vitamin D also plays an important role in reducing chronic inflammation and plays a major role in the probability of deactivating inflammatory cytokines which are linked to insulin resistance and thereby enhancing calbindin expression which

involves protection from cellular suicide (apoptosis). Proper dietary management is one of the appropriate ways which can produce sustain reduction in weight, fibrosis, inflammation, etc., in patients who are suffering with both NAFLD and type 2 diabetes.

The summary of sources, uses and abnormalities of diet in the NAFLD were shown in the Table 1 and Diet management in NAFLD was shown in Figure 2.

Lifestyle modification in management of nonalcoholic fatty liver disease and type 2 diabetes

At present, weight loss is the cure of choice to reduce hepatic fat accumulation and reduce the advancements of fibrosis and inflammation. Lifestyle modification is one of the possible ways to reduce weight which include programmed diet and physical exercise, which are very effective treatment options for patients who are suffering with NAFLD and type 2 diabetes. Lifestyle modifications are advantageous in patients with NAFLD, improving not only liver disease but also atherogenic dyslipidemia, blood pressure levels, and hyperglycemia [105-107]. The effectiveness of lifestyle modification on improving various markers of NAFLD (steotosis, presence of NASH, reduction of circulating liver enzymes) was recently explained in a systematic review of 22 randomized clinical trials with 2588 patients with NAFLD [108]. However, much information is not available about the long-term effects of lifestyle modification on liver histology, on the least amount of weight loss required to attain such histological benefit and on best approach to maintain it over long time. In imaging studies, relative depletion in hepatic steatosis achieved through lifestyle modification has been usually in the range of ~40%–50% and absolute changes have often been small on the order of ~5% [105,106,109].

Type 2 diabetes algorithm "Lifestyle development is necessary for all patients with diabetes. In obese patients who are suffering with prediabetes and type 2 diabetes weight loss should be considered to reduce their weight. The need for medical therapy should not be elucidated as a failure of lifestyle modification, but as a complement to it". A type 2 diabetes patient with NAFLD tends to consume more calories and takes part less in physical activities. In fact, data from the Nutrition Examination and National health survey

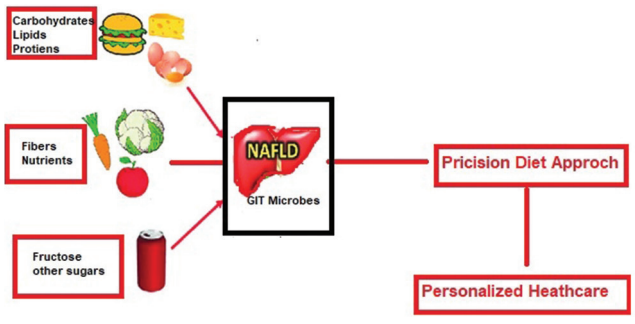

Figure 2: Role of diet in the management of nonalcoholic fatty liver disease

demonstrated that when patient with NAFLD have concomitant diabetes, they participate less in physical activities [110]. Similar to diabetes, the 1st tool which is used in the management of NAFLD should be sustained reduce in weight through lifestyle modification by proper diet and exercise. Moderate weight loss of 3%–5% of total body weight helps to reduce hepatic steatosis, weight loss of 7%–9% is necessary to reduce inflammation, and weight loss of 10% or more is required to reduce regression of liver fibrosis [111].

In some studies, it is mentioned that orlistat (tetrahydrolipstatin) which is a drug used to treat obesity has reported better histological improvement corresponding to the amount of weight reduced [112,113]. Thus, pharmacological agents which cause weight loss should always be considered especially when lifestyle intervention is failed. Pharmacological agents which cause weight loss should always be considered, especially when lifestyle modification is failed. Thus, it indicates that there may not be a lifestyle modification strategy which is better than the rest, and weight loss should be the primary aim. For example, physical training and aerobic exercise intervention achieving similar weight loss were equally essential in decreasing liver triglyceride content by ~30% among patients who are suffering with type 2 diabetes and NAFLD [114]. The following methods are included in performing physical training and aerobic exercise: 60 min of aerobic exercise per session by participants at 60%–65% of heart rate reserve, according to Karvonen formula (Target heart rate = [(max HR − resting HR) × % intensity] + resting HR) [104]. Aerobic exercise is performed on cycle, elliptical machines, treadmill and the participants can change their cardiovascular equipment from one session to the next session as they wish. Participants perform physical training which includes 9 different exercises like major muscle groups of weighing machines (vertical traction, chest press, shoulder press, leg extension, abdominal crunch, leg press, leg curls) and free weight (abdominal, biceps). Participants perform 3 sets of 10 repetitions after a learning phase at 70%–80% one-repetition maximum; with 1-minute rest period between each set.

However, some studies show that even with minimal weight loss steatosis reduction can be achieved, specifying that other determinants may play minor role in NASH improvement [105,106]. For example, several small (n = 18–45) and short-term studies (4–24 weeks) reported a moderate decrease in intrahepatic triglyceride accumulation by 1H-magnetic resonance spectroscopy (~15%) after physical exercise without any significant reduce in weight [114]. Dietary supplements, such as Vitamin D, have also been recommended for treating patients with NAFLD, but unsuccessful to show any consistent associations with liver triglyceride accumulation or NASH [115,116]. Clearly, more studies are required to completely understand the role of lifestyle management in treating patients with NAFLD and type 2 diabetes.

Bariatric surgery and nonalcoholic fatty liver disease

Bariatric surgery means a gastrointestinal surgery which helps to reduce weight in obese patients. A meta-analysis of

Table 1: Sources, uses, and abnormalities of diet in the nonalcoholic fatty liver disease

Types of diet	Source	Required quantity (%)	Uses	Abnormalities	References
Carbohydrates	Vegetables, fruits, whole grains, legumes, dairy products, sugar, meat and meat products etc.	45-60	Reduced body fat percentage, insulin resistance, waist circumference etc.	Liver is considered as the site for fructose metabolism, where as 60% oxidation of fructose consumption takes place. Compared to glucose metabolism, fructose metabolization is much higher in the liver. In adult patients with NAFLD increase in fructose intake lead to fibrosis and swelling	[124]
Fatty acids	Monounsaturated fatty acids (olive oil, nuts and avocado etc.) and omega-6 polyunsaturated fatty acids (vegetable oils like soya, cotton, sunflower and corn)	<30	In monounsaturated fatty acids phenolic compounds show anti-inflammatory and anti-oxidant properties which may produce an improvement in endothelial dysfunction and dyslipidemia	Since, omega-6 polyunsaturated fatty acids change the production of inflammatory markers and is more liable to oxidative degradation of lipids which leads to cell damage due to these all conditions excessive intake of omega-6 polyunsaturated fatty acids are reduced. Higher monounsaturated fatty acids consumption leads to decrease in risk of metabolic syndrome and cardiovascular disease. According to a systemic review (9 trails) including 1547 patients who are suffering with type 2 diabetes, estimated the effect of monounsaturated fatty acids in blood glucose control	[125-128]
Proteins and amino acids	Vegetables, fruits, vegetable proteins (whole grains, legumes etc.), animal proteins (dairy products, meat and meat products etc.)	15-20	Energy is essential for amino acids catabolism, subsequently; high protein consumption may lead to an increase in hepatic lipid oxidation which explains the important role of vegetable proteins in NAFLD. Some experimental studies states that taurine which is a nonessential amino acid and also a bile acid conjugate plays an important role in reducing hepatic lipid accumulation, inflammation etc.	In some studies, it has been mentioned that there is an inverse connection between vegetable proteins and NAFLD assessed by FLI, whereas positive association was seen in case of animal proteins with NAFLD. High protein diet is associated with an increase in risk of certain heart disease and cancer. In diabetes condition excessive intake of protein and low insulin level may cause increase in conversion of proteins to glucose, which may cause negative impact on blood glucose control	[129,130]
Vitamin D	Fatty fish (tuna, salmon etc.), fortified food (soya milk, orange juice, cereals etc.), shitake mushroom, sunlight etc.	20-40	Vitamin plays an important role in enhancing the liver enzymes and pro-insulin cytokines in NAFLD patients. Along with lifestyle modification Vitamin D supplement improves serum level biochemistry in NAFLD patients. It also reduces neuroinflammation, steotosis, and enhance hepatic insulin sensitivity and hepatic inflammation. An adequate amount of Vitamin D level may also enhance insulin resistance pathways connected with diabetes	Low Vitamin D levels can cause impaired glucose tolerance, damages the transcription function of pancreatic genes, and reduces insulin sensitivity, functioning of pancreatic B-cells and insulin synthesis and production	[131-133]

NAFLD: Nonalcoholic fatty liver disease, FLI: Fatty liver index

136 studies was performed by Buchwald *et al*. that estimated the effect of bariatric surgery on metabolic results and announced a complete resolution regarding type 2 diabetes which is seen in >75% patients who are suffering with diabetes and reduction in weight up to 60%.

NAFLD is linked with obesity and type 2 diabetes and the procedure used in improving obesity and type 2 diabetes by following bariatric surgery plays a key role in the resolution of NAFLD. Bariatric surgery not only plays an important role in the substantial weight reduction in NAFLD patients, but also through contemporaneous effects on important inflammatory and lipid metabolic pathways which are involved in the NAFLD pathophysiology [117-119]. Bariatric surgery enhances some changes in 3 main metabolic areas controlling NAFLD: improved lipid metabolism, reduced inflammatory activity and improved glucose homeostasis.

Long term-studies have stated that the metabolic benefits of bariatric surgery continue for a wide period. 5 years fallow

up of obese patients who are allocated to bariatric surgery which resultant to enhanced diabetic control and wight loss. Retrospective surveys of a larger unit of patients who have undergone sleeve gastrectomy have been found to regain weight at 3 and 5 years after the surgery and endurance of diabetes is some patients. RYGB (Roux-en-Y gastric bypass) has been recently surpassed as one of the most common bariatric surgeries performed and can reduce inflammation, fibrosis and steatosis. RYGB and SG procedures involve in the glycemic control which is following three primary mechanisms such as early enhanced hepatic insulin sensitivity because of postsurgery caloric restriction, late enhanced peripheral insulin sensitivity because of reduction in weight and enhanced postprandial insulin secretion because of increase in glucagon-like peptide 1 secretion.

In line with these findings, large amount of weight loss is obtained after bariatric surgery, which is showed in most of patients and they experienced inhibition of fibrosis (~65%), steatohepatitis (~80%) and steatosis (~90%) [120], Therefore, these results were recently confirmed in a study where ~50% patients showed better results in fibrosis scores. The magnitude of fibrosis depletion depends on the baseline severity of liver disease, with no development in fibrosis observed 5 years after bariatric surgery in a large unit of patients (n = 381) with mild liver disease [12,121].

Most of the bariatric surgery studies have some limitations. These studies lack standardization of the preoperative very low caloric diet management and postoperative dietary management about how the intraoperative liver biopsy sample is obtained. Moreover, the repeat post bypass liver biopsies are usually carried at varying intervals over time. Finally, most of the studies have not been controlled, and therefore they were potentially at risk for patient selection bias. It is also not clear that whether changes in liver disease are simply the result of weight reduction or whether bariatric surgery has an intrinsic metabolic effect on the liver. Well-designed prospective studies are required to govern the ideal patient, long-term efficacy, type of surgery and safety of bariatric surgery in NAFLD [122,123]. Different therapeutic approaches for the management of NAFLD were shown in the Figure 3.

Conclusion

From the above studies, it is clear that increasing physical activity or exercise is effective in improving metabolic parameters in patients who are suffering with both NAFLD and type 2 diabetes. Proper dietary management leads to weight loss are also effective in improving metabolic parameters in patient with both NAFLD and type 2 diabetes. Comparing treatment approaches in patients with both NAFLD and type 2 diabetes is required to develop future cost-effective treatment strategies. Future studies should employ accurate methods to establish the most effective means of producing a sustained reduction in liver fat, fibrosis, inflammation etc., and report their interventions. Such interventions play an important role in deciding upon future treatment approaches for patients with both NAFLD and type 2 diabetes.

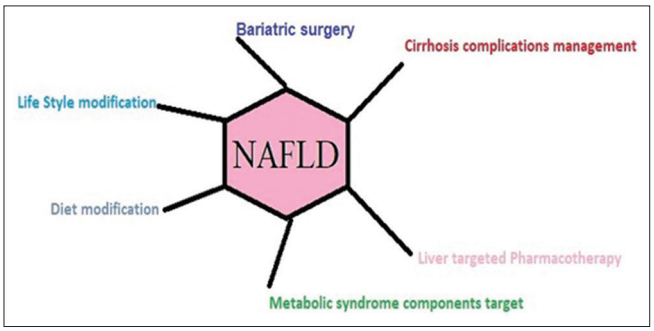

Figure 3: Different therapeutic approaches of nonalcoholic fatty liver disease

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Conflicts of interest

There are no conflicts of interest.

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