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Review on Non-alcoholic Fatty Liver Disease: Pathogenesis, Management and Treatment

Sayali V. Kathale[1*], JV Vyas[1]

1.Department of Pharmacology, Vidya Bharati College of Pharmacy, Amravati University, Amravati (MH) INDIA 444602.

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a metabolic syndrome and major chronic liver disease that can lead to liver cirrhosis, liver cancer and ultimately death. Although its progression rate may be slower than that other types of liver disease and the incidence of which is rising rapidly due to the increasing epidemic of obesity in both children and adults, worldwide. The accumulation of fat followed by subsequent inflammation is central to the development of liver injury, and is influenced by host factors including age, gender, presence of diabetes, genetic polymorphism and recently gut microbiome. NAFLD is also a risk factor of cardiovascular disease, which is the commonest cause of mortality. The natural history of NAFLD remains unclear. Lifestyle modification that including diet, exercise and weight reduction may be the best way to manage disease and one of the best advice for patients. This review focusses on the pathogenesis and evolution of new approaches to the management and treatment of NAFLD.

Keywords: non-alcoholic fatty liver disease, obesity, fibrosis, steatosis, insulin resistance.

*Corresponding Author Email: Sayalikathale2205@gmail.com

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INTRODUCTION

Obesity has become an important public health problem in many countries (1,2). Extreme obesity has received the attention in clinical setting, most obesity can be described as moderate to marked. However, moderate obesity contributes to chronic metabolic disorders, such as glucose tolerance, insulin resistance syndrome, dyslipidemia, hypertension, non-alcoholic steatohepatitis, central obesity (intra abdominal fat deposition) (3-5). In this review the main purpose is to explore whether the environmental factors contributing the development of obesity and abnormalities of insulin resistance syndrome (6,7). The consumption of fat in industrialized countries, due to intake of high fructose fruit drinks, baked goods, carbonated- beverages and candies (6,8).

The NAFLD is to describe a condition of fat accumulation in the liver without consumption of excessive alcohol and other specific causes of hepatic steatosis. In the case of NAFLD its aetiology is not yet completely understood, it is related to presence of insulin resistance and initial part of the metabolic syndrome (MS), and obesity, dyslipidaemia. The secondary causes of non-alcoholic steatohepatitis are relevant causes, like malnutrition, rapid weight loss (nutritional), lipodystrophy (metabolic) and drug-induced as well as other conditions such as inflammatory bowel disease, occupational exposure, bacterial overgrowth (9-12). NAFLD is a morphological pattern of injury of liver which non-alcoholic patients. Which is represent a form of chronic liver disease currently known as non-alcoholic steatohepatitis (NASH). NASH was first described by Ludwig et al (13,12). Cirrhosis is known complication reported that in 7%, 15%, 16% of patient with NASH. There is no histopathological “markers” patients at risk for progression to cirrhosis (13,14). currently no treated options specifically for NASH but this type of disease is usually managed and prevented with various types of lifestyle changes like weight loss, diet, exercise, but, again in absence of clear guidance, this is highly variable (15-18). Progression of NAFLD from hepatic steatosis, through inflammatory non-alcoholic steatohepatitis to fibrosis and cirrhosis (19-22). People with NAFLD will die from hepatocellular carcinoma (HCC) or need a liver transplant. The average age of people with NASH- cirrhosis is 50-60 years and the people with NASH is 40-50 years. Some studies showing that 38% of obese children have evidence of NAFLD (18). Emerging the drivers of the key features of NASH are cytokines, adipokines and cells of the innate and adaptive immune system enable cross-talk between the adipose tissue and the liver and interaction of free radicals with cellular constituents may result of peroxidation deterioration leading to an impaired of cellular functions (23-27). Representative data from the united states indicate that 19% Americans may have NAFLD (28-30). The molecular mechanism of NAFLD progression involves

a two-hit theory like lipid accumulation in hepatocytes called “first hit” and insulin resistance, oxidative stress, and cytokine production is called “second hit” (31,32). Physicians and patients should be equipped with the knowledge regarding this disease with the growing epidemic of this disease. The main aim of this review is to discuss the pathogenesis, history of NAFLD, diagnosis, risk including NAFLD as well as treatment options that is available for the management of NAFLD (33).

Symptoms, Risk factors Associated with NAFLD

NAFD usually causes no significant signs and symptoms some possible signs and symptoms of cirrhosis include: Abdominal swelling, enlarged breasts in men, enlarged spleen, red palms, enlarged blood vessels, yellowing of the skin and eye. Signs of NAFLD are enlarged liver, fatigue, pain in the upper right abdomen. Also the various causes of NAFLD and NASH like overweight or obesity, insulin resistance, high blood sugar, high levels of triglycerides. A wide range of diseases can increase the risk of NAFLD which including: high cholesterol, high levels of triglycerides in the blood, metabolic syndrome, obesity, polycystic ovary syndrome, type 2 diabetes mellitus, hypothyroidism, hypopituitarism, sleep apnea. Insulin resistance helps to central development of NAFLD, which represent that the hepatic manifestation of metabolic syndrome. Features of MS are at high risk for NAFLD (34-36). Excessive body mass index (BMI) is the most common risk for NAFLD (37-39). Type 2 diabetes mellitus is the high prevalence of NAFLD. In this context type 2 diabetes and NAFLD can almost develop simultaneously. In dyslipidemia low serum high density lipoprotein and high density lipoprotein levels are common in NAFLD patients. NAFLD may vary according to the age, sex and also ethnicity. The prevalence of NAFLD and stage of liver disease both appear to increase with age (37,40,41,45).

Clinical disease progression and Mortality

NAFLD is disease that has very different clinical manifestations and different rates of disease progression. Environmental factors which helps to progression of NAFLD are microbiome, metabolism, comorbidities and genetic risk factors. The patients with NASH are asymptomatic without clinically relevant outcomes for decades, but some can rapidly progress (42-44). Patients with a reference population mortality increased has been shown in several studies comparing NAFLD (46,47). In this disease the main cause to increase death in follow-up studies with biopsy-proven NAFLD is cardiovascular disease and liver related complications are using the third cause of death with increase in risk. The increased risk of mortality in NAFLD was confirmed in a meta-analysis. In newly published meta-analysis, the increase mortality of NAFLD patients, majority

were diagnosed with ultrasonography, could not be confirmed. Meta-analysis including 34 studies, no increase in CVD mortality was mainly observed (46,48).

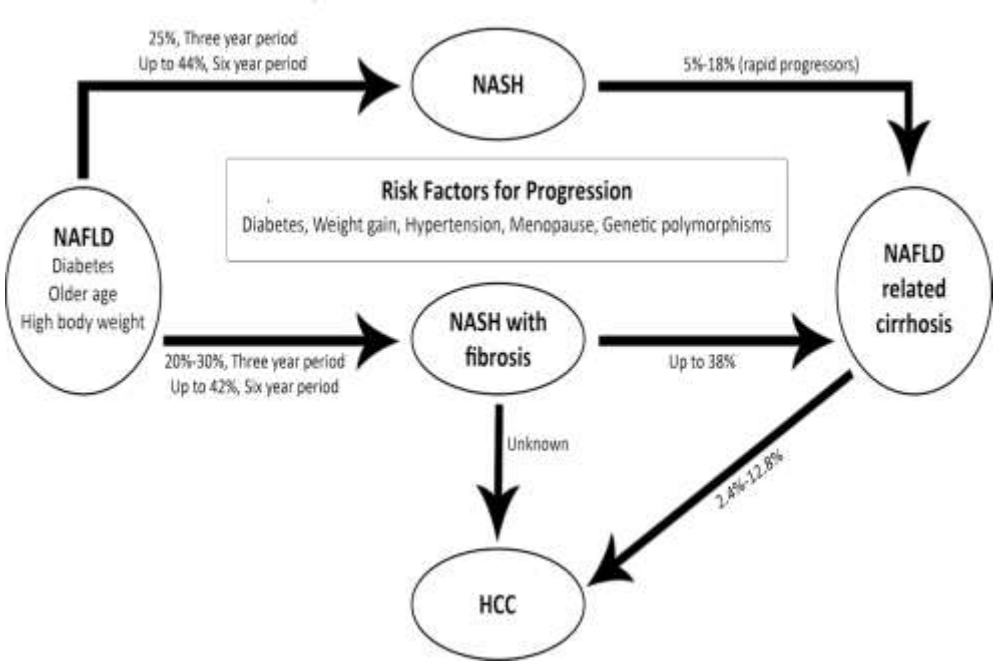

Figure: Overview of the progression of nonalcoholic steatohepatitis (NASH) to nonalcoholic fatty liver disease (NAFLD) and increased risk of hepatocellular carcinoma (HCC).

Epidemiology and Natural History of NAFLD

With an increasing of NAFLD and NASH accompanying the obesity epidemics, when NAFLD has a major impact on public health. The understanding of the natural history of NAFLD has been increase in the past decade. Dr sherif and colleagues revisit the epidemiology of NAFLD a focus of minority populations within USA. natural history of NAFLD which mainly depends on the histologic subtype of NAFLD. Those who have FL have a prognosis, whereas those who have NASH can have progressive fibrosis leading to cirrhosis. Improvement in fibrosis is documented at the precirrhotic stages. The patient who are first diagnosed with FL or FL-NI can progress to NASH and varying degrees of fibrosis, including cirrhosis, albeit at a slow rate. The authors highlight the difference in NAFLD prevalence, which reflect common history in same disease. Drs. McCullough and Goh describe the natural history about NAFLD with a long term liver related outcomes. NAFLD can develop to NASH and then progress to liver cirrhosis, the presence of liver fibrosis is the single based indicator of liver related mortality. The liver cancer is rising at an alarm rate, becoming increasingly in patients with NAFLD. Drs. Reeves, Zaki and Day describe the risk of liver cancer. Dr. Mantovani and colleagues summarize knowledge regarding associated between

Coronary artery disease and NAFLD and also knowledge with functional and structural cardiac abnormalities (49-51).

Pathogenesis

Understanding the pathogenesis of NAFLD and NASH is essential for proper therapeutic interventions (52,53). NAFLD is a metabolic syndrome, and its pathogenesis involves the complex interaction among hormonal factors, genetic factors and nutritional factors however, NAFLD or NASH is so complicated disease that it has been designated as "multiple hit and organ theory" (52,54). For several years to explain NASH pathogenesis a "two-hit" theory was posited. In this two-hit theory suggests that in the setting of NAFL alone (i.e., steatosis), a second 'hit' from other factors like oxidative stress was helps to development of NASH. It is not even certain whether NASH and NAFLD is always developed by NAFL. Mechanisms of the disease and their clinical manifestations are both highly heterogeneous. Pathogenic drivers are not likely to be identical in all patients.In pathogenic drivers of NAFLD and NASH is that the liver's capacity to handle the primary metabolic energy substrates, carbohydrates, and fatty acids and leading to accumulation of toxic lipid species. This type of metabolites induce stress, hepatocellular injury, and also death. When fatty acids sources in hepatocytes is essential for understanding the metabolic underpinning of NASH. fatty acids are supplied in excess and disposal is impaired, that they substrates the generation of lipotoxic species and provoke hepatocellular injury and ER stress (42,55).

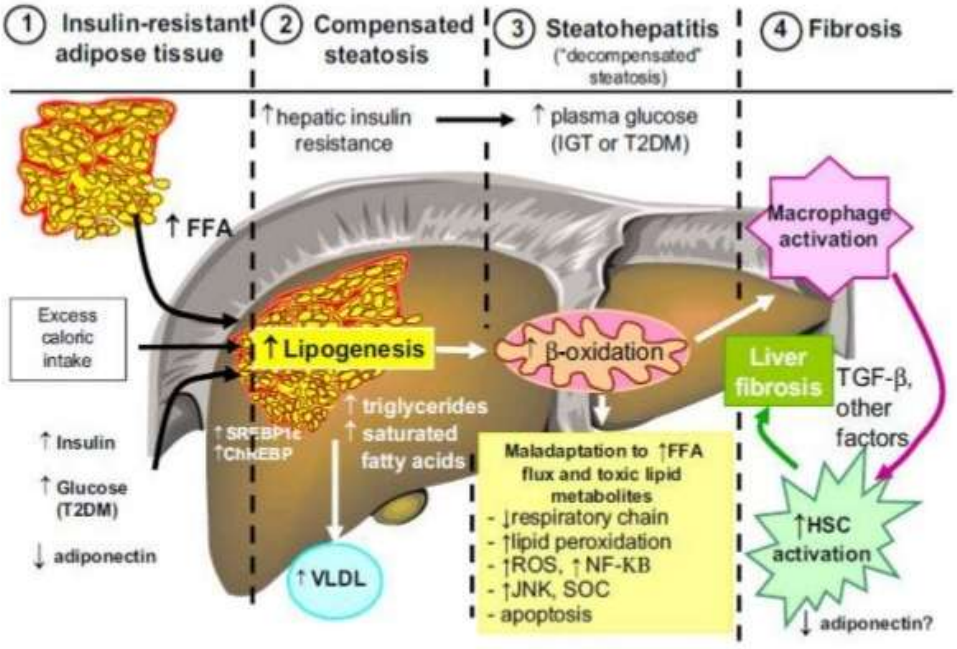

Figure: Pathogenesis of NAFLD

Sources of fatty acid in liver: it is an initial step in NAFLD pathogenesis is triacylglycerol accumulation in hepatocytes. TGA is synthesized from glycerol. Fatty acid absorbed in to the hepatocytes. Fatty acid usually produced from glucose in the liver via de novo lipogenesis. By β-oxidation in the mitochondria or peroxisomes fatty acid primarily catabolized and excess amounts are converted into TGA and its stored as lipid droplets in hepatocytes. Those pathways can result in hepatosteatosis. De novo lipogenesis, which strongly regulated by insulin through activation of transcriptional factor sterol regulatory element-binding protein. This mechanism explained the close relationship between insulin resistance and NAFLD/NASH. 60% of FA in the liver originates from white adipose tissue, adipocytes dysfunction may lead to overflow of FA and produced NAFLD or NASH (53,56,57).

Response to lipotoxic lipids: Hepatocellular injury in NAFLD is mainly characterized by endoplasmic reticulum (ER) stress, unfolded protein response, inflammasome activation, activation of apoptotic pathways and the certain lipids can be very harmful to hepatocytes in NAFLD (59). External factors which includes dysregulation of cytokines and adipokines, ATP depletion, uric acid toxicity and sleep apnea and also gut microbiome (42,58).

The inflammasome: Hepatocyte inflammasome activation may be important between the initial metabolic stress and stimulation of fibrogenesis in NASH and also subsequent hepatocytes death. Inflammasome is a multiprotein cytoplasmic complex that responds to danger- associated molecular patterns(DAMPs). This context included saturated fatty acids product of pathogen-associated molecular protein (PAMPs) which are product of gut microbiota and which delivered to liver in the portal circulation (60).

Insulin resistance: Insulin resistance is a characteristic feature of NAFLD and is caused by a variety of factors, include soluble mediators derived from immune cells and adipose tissue, such as TNF-α and IL-6 leads to inappropriate release of fatty acids through dysregulated lipolysis that further contributes to impaired insulin signalling throughout the body. Effect is known to promote insulin resistance, underscoring the important cross talk between metabolic dysregulation in NAFLD and liver (42).

Microbiome: NAFLD increase in the past 25 years in the developed world has been largely attributed to both a diet that rich in fructose, saturated fat and sucrose. Also the reason to increasingly more sedentary lifestyle. Risk factor involve in NAFLD may be evolution of the human microbiome, both the changing diet as well as use antibiotics in farm animals and also indiscriminate prescription of antibiotics to humans (42). Human studies gut microbiota was first fount to be altered in patients with chronic liver disease more than 80 years ago. In recent year gut

microbiota has gained much more attention due to advancement of high throughout next generation sequencing technology. In gut microbiota several mechanisms involved in pathogenesis of NAFLD are (1) Increase the production of gut short chain fatty acid and absorbed it Altered dietary choline metabolism. (2) Bile acid pools by microbiota. (3) Increased delivery of ethanol which derived from microbiota to liver. (4) Permeability of gut and release of endotoxin. (5) Interaction between microbiota and specific diet. Microbiome is nascent and considerable progress in linking its role to NASH is anticipated (61,62).

Mechanism of fibrogenesis: The accumulation of extracellular matrix in the liver, which leads to increase fibrosis, cirrhosis, portal HTN and liver failure, is the major cause which related to death in patient with NASH/NAFLD (42,63). Fibrogenesis is the damaged hepatocytes and immune cells activated also promote hepatic stellate cells activation. It is driven by signalling from stress or injured hepatocytes and which activated macrophages, leading to activation hepatic stellate into microfibroblasts. This mainly produce matrix proteins faster than they are degraded. Although hepatic stellate cell activation is a key event in liver fibrogenesis., it is mainly in the perisinusoidal space is relatively specific to steatohepatitis (52, 64, 42, 65).

Diagnosis

NAFLD is asymptomatic disease and is not recommended in general population (66). The diagnosis of NAFLD is established by presence of a pattern of steatosis, inflammation and hepatocellular injury on the liver biopsies in absence of significant alcohol consumption. Establishing a diagnosis of NASH is that it identifies individuals who are at risk for increasing liver disease to the point of cirrhosis and death from chronic liver disease (67). Clinicians should consider a diagnosis of NAFLD with abnormal liver tests and presence of one or more metabolic risk factors indeed the likelihood of NAFLD increases proportionately with the number of metabolic syndrome factors present. A scoring system was needed that include the spectrum of NAFLD and which would be sensitive to changes in the underlying disease process independent of the diagnosis of NASH. it is considered that incident discovery of elevation of liver enzyme levels or when hepatic steatosis is noted on imaging like ultrasonography (68).

To diagnose the non-alcoholic fatty liver, some factors included like medical history, conduct a physical exam, laboratory studies and also one or more tests.

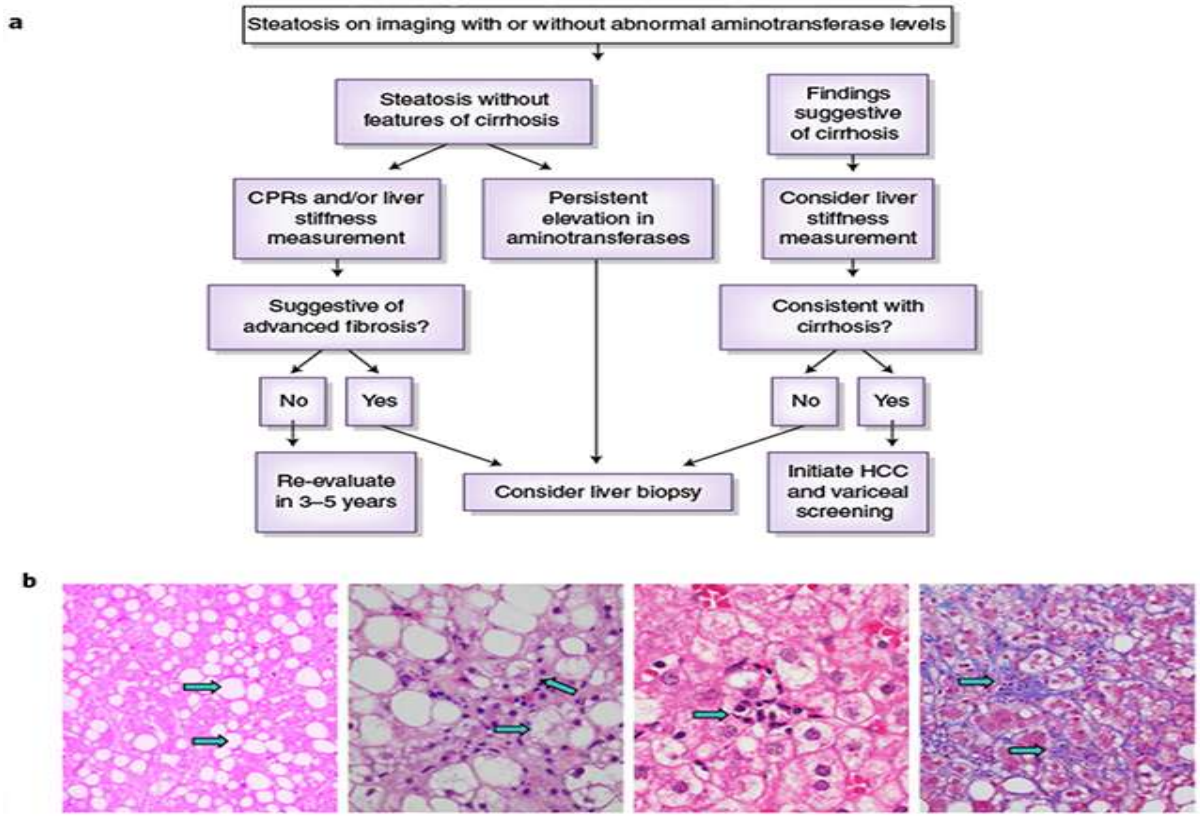

Figure: **Histological features of human NASH. a. A schema for diagnosing NAFLD and NASH. b, the images from liver biopsies demonstrate the typical appearances of macrovesicular steatosis (fat), hepatocellular ballooning, inflammation and fibrosis (arrows).**

Medical history and physical examination: Symptoms of NAFLD is include right upper quadrant pain, jaundice etc. liver injury commonly caused by excessive consumption of drug and alcohol. The history of the patient should explore diet, weight, physical activity, weight gain or loss i.e. changes in weight and also the previous medical history of patient i.e. assessment of associated conditions like diabetes, hypertension, hyperlipidemia, obesity and sleep apnea. The patient's family history should be check for the risk of cardiovascular and metabolic disorders and also the risk of chronic liver disorders. Also the signs should be obtained including blood pressure, BMI, weight, waist circumference this vital signs of patients are important to diagnose the NAFLD. Physicians should assess the risk factors of NAFLD including blood transfusion, sexual activity and also intervention of drug use (69).

Laboratory examination: In many cases, NAFLD disease is diagnosed after blood tests which show elevated liver enzyme. A diagnosis of NAFLD requires imaging or histology and other causes of liver disease have been excluded. If abnormal LFTs, this is raised transaminase s (ALTA – aspartate transaminase (ASTA) or gamma-glutamyl transferase. In histological findings the ALT

values do not correlate and unhelpful in diagnosis of NAFLD. A new approach is needed to use metabolic risk factors and to identify NAFLD rather than relying on liver disorders (70,71).

Antibiotics are also detected low titre in subjects with NAFLD or anti-smooth muscle antibody and assessment in normal IgG levels and do not indicate autoimmune hepatitis. If there is uncertainty about diagnosis of NAFLD then a liver biopsy should be considered. NAFLD liver fat is calculated with the help of presence of the fasting serum AST and ALT ratio fasting serum insulin, type 2 diabetes mellitus. Score does not properly distinguish between the different stages of NAFLD OR NASH.

Imaging for steatosis and inflammation: First line investigation for hepatic steatosis ultrasonography is widely used that mainly provides assessment for fatty infiltration of the liver. It is very effective and commonest modality for diagnosing liver steatosis of hepatocytes are steatotic but can be unreliable with lesser degrees of steatosis. Ultra sound scan is widely used due to its simplicity and low cost. Other imaging modalities such as Magnetic resonance imaging (MRI) or CT techniques and magnetic resonance spectroscopy can also use to detect lower levels of steatosis but they are not routinely used in the assessment of steatosis. MRI also identify changes in fat content accurately. Magnetic resonance imaging estimated proton density fat fraction which correlates strongly with MRS measured liver fat and histologically determined steatosis grade. Magnetic resonance imaging is another technique under development and involves a three-stage process. 1. Mapping for inflammation imaging, 2. Mapping for liver iron quantification for liver fat quantification. The fibroscan device use with controlled attenuation parameters (CAP) which can be assess hepatic steatosis. Controlled attenuation parameter is a new ultrasound technique with assessment of liver stiffness (65,72).

Imaging for fibrosis: Transient elastography (TE), through assessment of liver stiffness measurement is most secondary and tertiary centres for assessment of liver inflammation. In NAFLD detection of significant fibrosis and cirrhosis mainly magnetic resonance elastography has also been useful. Most elastography modalities the presence of significant inflammation can increase elastography reading (65,73).

Liver biopsy: Liver biopsy is very essential for the diagnosis of NAFLD and its reliably differentiates NAFL from NASH (74). liver biopsy may not affect treatment decisions, its remains the determination of steatosis and also maintain standard of diagnosis as well as the grade of inflammation and also stage of fibrosis (66). It is a gold standard for characterizing liver histological alteration patients with NAFLD. Biopsy is very expensive but carries morbidity and low mortality risk. It should be considered in NAFLD patients competing etiologies for HS and the

severity of coexisting CLDs cannot be excluded without a liver biopsy (37). During liver biopsy insert a needle in the liver and remove or collect the piece of tissue for examination or observation, this test can help to determine liver scarring. Liver histology remains for outcomes in clinical trials and is required for seeking regulatory approval of new therapies (65).

Management and treatment of NAFLD

All the patients with NAFLD which needed advice about lifestyle modification includes weight loss, physical exercise also the treatment of metabolic risk factor like diabetes mellitus, dyslipidaemia and hypertension. Management of NAFLD mostly depends on the stage of disease, and the importance of careful risk stratification. Management strategies of NAFLD there are four main areas to focus: target components of the metabolic syndrome, modification in lifestyle, managing the complications of cirrhosis. Patient with fibrosis are risk of developing liver disease so require more lifestyle modification if this modification is fails can be considered for liver directed pharmacotherapy (75). The main purpose of management of NAFLD there are three types of modalities of therapy includes lifestyle modification, pharmacotherapy and bariatric surgery. Lifestyle modification is applicable in all types of NAFLD related stages but pharmacotherapy and bariatric surgery should not be considered for patient with simple steatosis. In biopsy proven NASH and hepatic fibrosis pharmacotherapy should be considered as per the guideline of American Association for the study of liver diseases (AASLD).

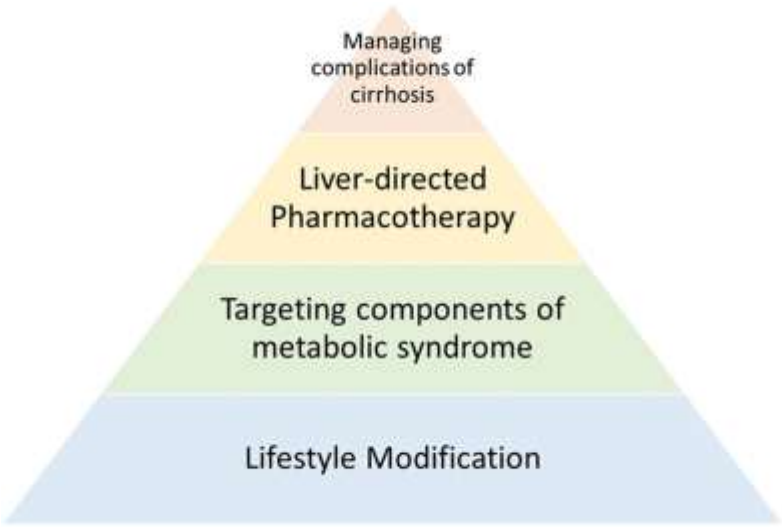

Figure: management strategies in non-alcoholic fatty liver disease (NAFLD) (management)

Lifestyle modification: Lifestyle modification of management of patient with NAFLD aimed at weight loss and increase regular physical activity or workout. Patients with NAFLD should be encouraged or motivate to avoid sedentary lifestyle by increasing daily activities, regular exercise and eating healthily. This lifestyle intervention including exercise, healthy diet can be very

effective to reducing body weight (75). Weight loss or physical activity improves patient's cardiovascular risk, improves steatosis and reduces hepatic inflammation and injury.

Diet: Encouraging data that diet induced weight loss may be very important to for patients with NAFLD, patients have difficulty maintaining weight loss. (76). Calorie-restricted diet should be advised to achieve their target weight. In weight loss diet some advice should include avoiding simple carbohydrate, saturated fats and sweetened food. Patient consume less n-3 PUFAs than controls. Supplementation with n-3 PUFA decrease liver fat but does not have statistically significant effect on ALT levels. Simple therapeutic option for NAFLD patient is dietary fish oil (77). A Mediterranean diet like high in monounsaturated fatty acid, as compared diet with a high in carbohydrates, has been reduce hepatic steatosis and also improving insulin sensitivity (75).

Exercise: Higher levels of habitual physical activity are associated with lower levels of steatosis. Increase skeletal muscle sensitivity with the help of Aerobic exercise thereby reversing insulin resistance, which is one of the key pathophysiological mechanisms which causing NAFLD. Improvement of liver enzymes, reduced steatosis and reduction in liver fat with the help of moderate intensity training, high intensity training and resistance exercise but the effect of histology remain unknown. All NAFLD patients should be advised to increase physical activity and exercise. Further evidence, one approach is mainly recommended 30min of moderate exercise five times weekly. Patient with NAFLD increase their daily step count to >10000 steps/day (75, 77).

PHARMACOLOGICAL MANAGEMENT

Anti-oxidants and cytoprotective therapies

Oxidative stress and free radical formation is helps to progression of simple steatosis (78).

Vitamin E: In different clinical trials vitamin E has been studied. It is a fat soluble vitamin, has an antioxidant property and two recently published, large, randomized control trials, PIVENS and TONIC, assessed its effect on adults and pediatric population respectively. Improvement of serum transaminases and liver histology in non-diabetic NAFLD patients in PIVENS trial, vitamin E 800 units per day was associated. In this trial fibrosis scores were not improved. Vitamin E supplementation in SELECT trials 400 units per day in healthy individuals was associated with significant increase in prostate cancer. Currently vitamin E supplementation 800 units per day is recommended in non-diabetic individuals with biopsy proven NASH (78, 79).

Betaine: Betaine has been shown to increase S-adenosylmethionine levels and reduce oxidative stress. It is a naturally occurring metabolites of choline. Unfortunately, betaine compared with placebo in a controlled trial, it failed to improve steatosis (79).

Ursodeoxycholic acid (UDCA): UDCA is also known as hydrophilic bile acid with cytoprotective and antioxidant properties and can improve serum transaminases in NAFLD but cannot alter liver histology (79).

Pentoxyphylline: Pentoxyphylline has been evaluated NASH for is important anti-inflammatory activity and also is a tumour necrosis factor alpha (TNFα) inhibitor. Some trials like a meta-analysis of randomized, double blinded, placebo-controlled trials showed that pentoxyphylline could improve the histological parameters in NAFLD patients and also reduce the aminotransferase activities (79).

Insulin sensitizers

Metformin: Metformin is a biguanide insulin sensitizing agent. Metformin is widely used in treatment of type 2 diabetes and also major action is mediated through activation of AMPK. This increase beta oxidation of FFA, improves glucose intake and reduce hepatic gluconeogenesis and lipogenesis. Metformin use to reserve for the management of patients with NAFLD and type mostly 2 diabetes.

Incretin-based therapy: It is a Glucagon-like peptide 1 receptor agonists, which not only improves insulin sensitivity but also causes weight loss by suppressing appetite and inhibiting gastric emptying (78). It is a gut derived neuro endocrine hormones, are produced by the intestinal tract in response to food ingestion. These drugs are licensed for management of type 2 diabetes. Circulating peptide-1 has a half-life due to rapid degradation by the enzyme dipeptdyl peptidase-4 and GLP-1 receptor agonists with increased DDP-4 resistance and DDP-4 inhibitors have been developed as therapies. It encouraging open- label studies controlled trials in NAFLD are underway (79).

Obeticholic acid (OCA): OCA is a farnesoid X receptor (FXR) which present in liver, kidney, adipose tissue and intestine, it is a nuclear receptor. FXR mainly controls the target gens in transport mechanism and bile acid synthesis and also carbohydrate and lipid metabolism. OCA which improved hepatic fibrosis and induced weight loss but resolution of NASH was not statistically more than placebo. Currently, it is not recommended in the routine management of NAFLD (78).

Thiazolidinediones (TZD): It is also called thioglitazones. TZDs are selective ligands of nuclear transcription factor peroxisome proliferator- activated receptor- gamma which is present in pancreatic β-cells, skeletal muscle, adipocytes, macrophages, endothelial cells. Its increased the fatty acid oxidation and subsequent lead to reduction in hepatic fat accumulation and these have been demonstrated to have potent benefits in pre-clinical models of NAFLD (78,79).

Lipid lowering agent

omega-3 fatty acids: omega-3 polyunsaturated fatty acid treatment improved hepatic steatosis also use to manage dyslipidaemia, which commonly found in patients with NAFLD. In NAFLD treatment there are no support direct benefit of those drugs but they will be used to reducing cardiovascular risk.

Statins: Statins are used for the treatment of hyperlipidemia. Hyperlipidemia seen in patients with NAFLD as a part of metabolic syndrome. Low moderate dose of statins has been found to be safe with low hepatic toxicity. Statins decrease hepatic transaminases and hepatic fat but have no effect on hepatic fibrosis (78).

Bariatric surgery

Bariatric surgery has been shown to reduce most of the histological features of NAFLD also obesity associated T2DM and IR. By bariatric surgery sustained weight loss is achieved. This surgery improved metabolic syndrome and reduce their mortality. At the present time there are various types of endoscopic procedures and bariatric surgery are available and approved for morbid obesity. In united states laparoscopic sleeve gastrectomy is most common. Any other surgeries include vertical band gastroplasty, gastric bypass, biliointestinal bypass, biliopancreatic diversion with duodenal switch and gastric banding. patients with cirrhosis of liver are higher risk for bariatric surgery. Bariatric surgery remains unclear how to improves insulin sensitivity but it is well recognized that surgery can improve overall metabolic syndrome (78- 80)

Liver transplantation

End-stage liver disease due to NAFLD liver transplantation is the only possible treatment. Post-transplant for such NAFLD patient are comparable to that seen with other indications, although likely reflects stringent case selection. Recurrence of NASH is common post-transplant due to the use of immunosuppression like corticosteroid, it rarely results in allograft loss (79).

CONCLUSION

NAFLD is the fastest growing cause of liver disease due to rising rates of obesity in both children and adult, worldwide shows no sign of waning. Recent trends in diet and lifestyle modification have increase the prevalence of NAFLD/NASH. in NAFLD simple steatosis vary from inflammation all the way through fibrosis and cirrhosis. Hepatic steatosis is recognized to be difficulties of complex interplay between environment, diet, adipose tissues, also a full understanding of its pathogenesis has not be explain. Understanding the cause of NAFLD and

designing rational will require continued research with collaboration among investigators in fields such as biophysics, pathology and biochemistry.

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