Obesity and Non-Alcoholic Fatty Liver Disease: Pathophysiology and Management Focused

Febyan and Norman Delvano Weky

ABSTRACT

The continuing rise of obesity epidemic in the global population has been markedly associated with the escalating occurrence and severity of non-alcoholic fatty liver disease (NAFLD). This condition represents a complex metabolic imbalance, primarily characterized by excessive intrahepatic accumulation of triglycerides, known as hepatic steatosis. This pathophysiological process is initiated by the disproportionation between the uptake of dietary fatty acids in plasma, as well as the increase of *de novo* fatty acid synthesis, which is not equally accompanied by the exportation and oxidation of fatty acid in the form of triglycerides. As mentioned earlier, the underlying metabolic process becomes a significant risk factor for developing cardiometabolic complications, involving type 2 diabetes mellitus, insulin resistance, and dyslipidemia. This review presents a comprehensive understanding of the pathogenesis and pathophysiology of obesity and NAFLD to determine innovative management approaches for the prevention and treatment of the disease.

Keywords: Non-alcoholic fatty liver disease, obesity, lipid, metabolic disorder.

Febyan*
Department of Medicine, Metro Hospital Jababeka, Cikarang, Indonesia.
(e-mail: febyanmd@ gmail.com)
N. D. Weky
Department of Medicine, Waikabubak General Public Hospital, West Sumba, East Nusa Tenggara, Indonesia.

*Corresponding Author

I. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases that ranges from simple steatosis to progressive inflammation and fibrosis in the liver organ [1]. One of NAFLD main hallmark features is its consistent association with the obesity epidemic [2]. Numerous studies have reported that obesity is an alarm sign of NAFLD, especially in Western countries [3]. Among European countries, elevating incidences of obesity have been reported, averaging from 10-40% in the past ten years, divided into 10-25% of men population and 10-30% of women population [4]. Meanwhile, about 64% and 50% of the United States population are currently estimated to be overweight and obese, respectively [5]. Obesity mainly leads to the progression of metabolic syndrome (MetS) and other comorbidities, including type 2 diabetes (T2DM), NAFLD, hypertension, hyperlipidemia [5]. Apart from life expectancy, obesity also essentially burdens the healthcare system [6]. The increased prevalence and severity of NAFLD have been correlated with the rising trends in the obesity epidemic worldwide [7]. In this review, the authors emphasize on discussing on the pathogenesis and management approaches of NAFLD. Hopefully, the clinicians will be able to determine an appropriate diagnosis and perform prompt treatment in obese patients with NAFLD.

II. NON-ALCOHOLIC FATTY LIVER DISEASE

Histologically, the definition of NAFLD is described by the pathological findings of $\geq 5\%$ of macrovesicular steatosis within the hepatocytes cells in patients with no significant alcohol consumption (≥ 30 g/day in men and ≥ 20 g/day in women) or no other known cause of chronic liver disease [1], [8]. Etiologies of NAFLD is generally initiated by multiple factors, including insulin resistance (IR), poor diet, and underlying metabolic disturbances [9]. Lifestyle-related factors like sleep deprivation, irregular food intake, sedentary activity, and excessive weight gain are also considered NAFLD risk factors [8], [9]. NAFLD is subdivided into the fatty liver without inflammation and non-alcoholic steatohepatitis (NASH). The disease often progresses to fibrosis, advanced cirrhosis, hepatocellular carcinoma (HCC), and eventually causes mortality [10], [11]. The diagnosis is gathered based on a collection of clinical signs and symptoms, laboratory tests, imaging studies, and histological findings (Table 1) [12].

TABLE I: NAFLD CLASSIFICATION BASED ON HISTOLOGICAL FEATURES

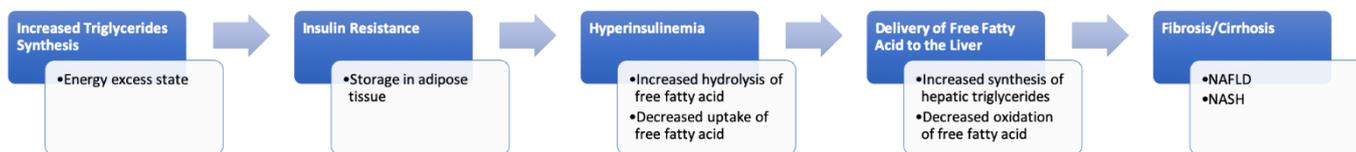| Classification	Histological Features
Class I	Simple fatty liver disease
Class II	Fatty liver accompanied by lobular inflammation
Class III	Fatty liver accompanied by lobular inflammation and ballooned hepatocytes
Class IV	Fatty liver accompanied by lobular inflammation, ballooned hepatocytes, Mallory-Denk bodies, and fibrosis (Stage 1-4)

Fig. 1. Triglyceride in NAFLD.

As clinicians, prompt and accurate therapeutic approaches must be established for the patient right after diagnosis. A novel and updated knowledge regarding NAFLD pathogenesis is needed to understand the phases and progressivity of disease and gain the purpose of expected therapy to be appropriately achieved.

III. THE UNDERLYING PATHOGENESIS OF NAFLD

Many studies have explained the underlying pathogenesis of NAFLD that is primarily related to several factors leading to hepatic steatosis, followed by "a second hit", leading to further hepatic damage progression. Advanced progression of NAFLD occurs after the accumulation of triglycerides (TG) within the hepatocytes cells. Triglycerides are an integral form with components formed from lipoprotein particles synthesized in the liver and small intestine. These substances are the source of stored energy in skeletal muscle and adipose tissue. Dietary free fatty acids (FFA) are released from adipose depots and are used for hepatic TG synthesis. In the hepatocyte, they will undergo oxidation of they become esterified into TG. A diacylglycerol acyltransferase (DGAT) is the enzyme responsible for catalyzing the final process of TG synthesis. Ultimately, TG will come out from the liver organ as very-low-density lipoprotein (VLDL) [14]. Accumulation of excessive TG in the liver indicates an imbalance among the uptake, synthesis, exportation, and oxidation of fatty acids [12]. In states of energy excess, the hepatic DGAT process and TG synthesis are increased. Triglycerides are exported from the liver organ in lipoprotein particles and derived to extrahepatic tissues [15].

In the adipose tissue, lipoprotein lipase hydrolyzes the liver-derived triglyceride and liberates FFA, which are subsequently transported into adipocytes. The FFA is derived from visceral adipocytes, reaching the liver through the portal vein, overload hepatocytes with lipid, and promote hepatic TG storage. Under the condition of insulin resistance, there is an increase in lipolysis in adipose depots and inhibition of FFA uptake, increasing FFA delivery to the liver. Fig. 1 illustrates the mechanisms of hepatic fat deposition [13]-[15].

Several animal model studies have demonstrated that inhibition of TG synthesis resulted in the improvements of hepatic steatosis. Surprisingly, a recent animal model showed that the TG synthesis provides a protective mechanism to limit the NAFLD progression into NASH and cirrhosis. The authors hypothesized that TG accumulation is a hallmark that the liver over-exposed to FFA and VLDL is a protective mechanism against NAFLD [14]. Alteration of adipocytokine secretion from adipocytes contributes to metabolic and inflammatory abnormalities, such as altering the synthesis rate of TG in the hepatocytes and increased lipolysis in central adipose tissue. As mentioned before, low circulating adiponectin levels are associated with several components of MetS [12]. In the liver, adiponectin escalates insulin sensitivity by reducing hepatic gluconeogenic enzyme expression and the rate of endogenous glucose production.

In addition, adiponectin suppresses lipogenesis and activates FFA oxidation [16], [17]. Tumor necrosis factor α (TNF-α) and adipocytes-derived cytokine are vital mediators of IR that impair insulin signaling by decreasing the tyrosine kinase activity in IR. Some studies showed that exaggerated activities of TNF-α plays a key role in the pathogenesis from NAFLD to HCC by increasing mitochondrial generation of reactive oxygen species (ROS), promotes hepatocyte apoptosis, and recruits inflammatory cells to the liver [11]-[17]. Therefore, some studies have reported that, in the animal model for NAFLD, fatty liver disease is significantly improved by inhibiting TNF-α production [18].

The adipose tissue secretes leptin in proportion to adipose tissue mass at the presence of leptin deficiency or due to leptin resistance, as generalized steatosis develops in some organs such as the liver, pancreatic islets, heart, kidneys, and muscle. Leptin functions as an anti-steatosis hormone that prevent FFA entry and fat accumulation in non-adipose tissues [19]. Moreover, leptin appears to be essential for developing fibrosis in response to chronic liver injury due to induction of transforming-growth-factor β1 (TGF-β1) [20].

The presence of NAFLD accompanied with other risk factors promotes more severe disease progression into NASH, especially those with MetS as classical symptoms. It proves that insulin resistance might play a role in disease progression [21]. On the other hand, oxidative stress has also been acknowledged as a mechanism responsible for NAFLD progression into NASH. The oxidative stress includes ROS production and lipid peroxidation, which eventually leads to NASH. The potential source for the ROS consists of the hepatic cytochrome P450 2E1 and mitochondria [22]. Mitochondrial damage also produces ROS, which may develop into NASH and fibrosis by lipid peroxidation and cytokine induction [23]. Oxidative stress in the liver occurs when there is excessive fatty acid oxidation [20]. Hepatic stellate cells are activated by stress during chronic liver injury and produce excessive extracellular matrix leading to fibrosis; additionally, they also produce ROS contributing even more to the oxidative stress [19]-[22].

IV. OBESITY-RELATED PATHOGENESIS OF NAFLD

Obesity seems to be assigned in both the primary process leading to NAFLD and its progression to NASH (Fig. 2) [24]. An adipocyte-like function has been attributed to hepatocyte, when the capacity of adipose tissue to store excess energy is diminished in common obesity [20]-[24].
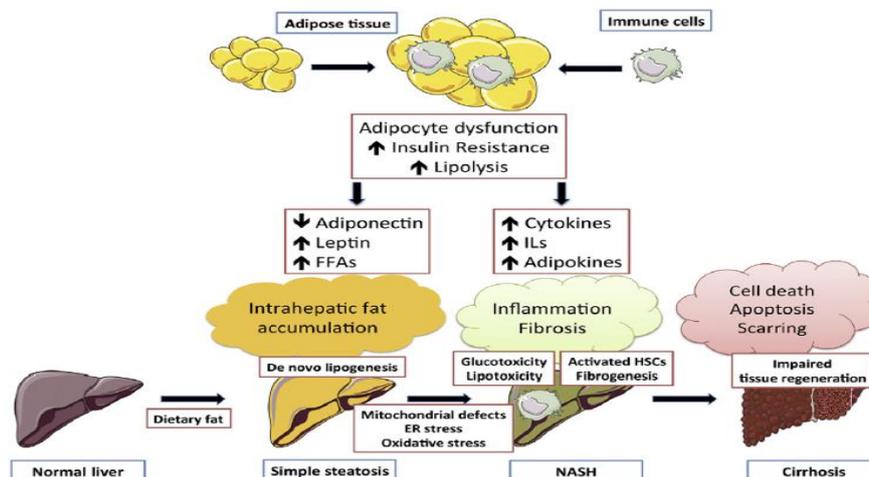
Fig. 2. Obesity in NAFLD.

There are two forms of toxicity condition, including lipotoxicity and glucotoxicity, with processes starting with the exposure of hepatocyte cells to a high amount of lipid and carbohydrate levels. They respectively play central roles in both the development of NAFLD and the subsequent progression to NASH. The pathogenesis of mechanisms involving lipotoxicity and glucotoxicity with NAFLD and NASH include mitochondrial defects, endoplasmic reticulum stress, and oxidative stress [25]. When obesity is not satisfactorily managed at the stage of NAFLD, an intrahepatic inflammatory process will start, possibly as a failed counter of regulatory effort to limit NAFLD [24]. This condition corresponds the low-grade inflammatory process that take places within the adipose tissue of the obese patients [26]. During this process, the hepatic innate immune cells, such as Kupffer cells, dendritic cells, and hepatic stellate cells (HSCs), are activated and the liver is progressively infiltrated by immune cells, including neutrophils, monocytes, T-lymphocytes, and macrophages [27]. Obesity also affects the liver through adipokines, such as leptin, adiponectin, and other hormones derived from the adipose tissue, contributing to NAFLD, NASH, and HCC [25]. Adipokines imbalance in obese patients, during the enlargement of adipose tissue, leads to the adipokines shifting towards a more steatogenic state, inflammatory, and fibrogenic profile.

The aforementioned condition starts from the adipose tissue diminishing its ability to store excess energy [21]. Adipocyte dysfunction and IR are increased, leading to lipolysis [23]. This state will affect the circulating FFAs, leptin increase, and adiponectin decrease, resulting in intrahepatic fat accumulation, which is further amplified by the high-fat diet and carbohydrate consumption (commonly among obese patients), subsequently aggregating *de novo* lipogenesis [25]. Upon the expansion of adipose tissue, infiltration of immune cells also occurs, resulting in the production of cytokines and interleukins [20]-[22]. At a certain stage when obesity happens at a stage where NAFLD is at risk to occur, an intrahepatic inflammatory process occurs at a low, but steady rate. The immune cells that infiltrate the liver also cause toxicities. Lipotoxicity and glucotoxicity are two components that play a major role in the deterioration of NAFLD, through the mechanism of mitochondrial defects, (endoplasmic reticulum) ER stress, and oxidative stress [24]-[27].

V. MANAGEMENT OF NAFLD

Non-alcoholic fatty liver disease patients without NASH or hepatic fibrosis are treated by lifestyle changes, including diet modification and moderate physical exercise and underlying causes. Pharmacological approaches are more recommended in the presence of NASH and fibrosis. National Institute for Health and Care Excellence (NICE) suggested that advanced liver fibrosis in NAFLD patients is an indication for pharmacotherapy agents [28]. Lifestyle modification can be considered as an effective therapy to prevent the progressivity of hepatic injury in NAFLD patients [29]. Diet modification, consisting of a low-calorie, low-fat, low-carbohydrate, and high-protein diet, called energy restriction strategies, can also be considered [1]. Based on the European Association for the Study of the Liver (EASL) and Asia-Pacific and The American Association for the Study of Liver Diseases (AASLD) guidelines, the Mediterranean diet is considered for NAFLD patients [1], [30]. The recommended deficit diet per day to induce a weight loss is 500-1000 g/week by 500-1000 kcal.

Furthermore, based on the Italian Association for the Study of the Liver (IASL), the recommended amount of fat and carbohydrate should be less than 30% and not more than 50% of total calories, respectively [2],[20]. The other option includes coffee consumption, which may be considered because it has been known for its liver-protective ability among NAFLD patients by reducing histological severity and liver-related outcomes and inversely related to the steatohepatitis severity [30]. Therefore, regular coffee consumption should be encouraged among NAFLD patients. Coffee intake should be $\geq$ 2 cups/day to improve NAFLD [31]. The mechanism of action is because caffeine works as an inhibitor of proliferation from hepatic stellate cell; thus, exerting an adenosine receptor inhibitor for its anti fibrogenic effect [32]. Other than that, fish oil or omega-3 fatty acid supplementation can be considered because it reduces hepatic steatosis and improves serum triglyceride, gamma-glutamyl-transferase, as well as high-density lipoprotein (HDL) in NAFLD patients [32]. Unfortunately, the AASLD guideline stated omega-3 fatty acid should not be used as a specific treatment of NAFLD or NASH, but it can be considered to treat hypertriglyceridemia in NAFLD patients [1], [30]-[34].

Non alcoholic fatty liver disease (NAFLD)

↓

Treatment of underlying causes (Diabetes mellitus, Obesity, Dyslipidemia, etc)

↓

NAFLD without non alcoholic steatohepatitis (NASH) and significant fibrosis

↓

Lifestyle modification:
A] Diet modification–
1. Energy restriction
2. Low calorie, low fat, and low carbohydrate diet
3. 500-1000 kcal deficit diet to induce a weight loss of 500–1000 gram/week
4. Coffee intake ≥2 cups/day improves NAFLD by inhibiting proliferation of hepatic stellate cell
5. Fructose-containing beverages and foods should be avoided
6. Avoid alcohol consumption
7. Omega-3 fatty acid supplementation may be a new treatment option for NAFLD but Omega-3 fatty acid should not be used as a specific treatment of NAFLD or NASH, but it can be used to treat hypertriglyceridemia in NAFLD patients

Plus

B] Physical exercise–
1. Both moderate- vigorous aerobic exercise

At least 3%-5% of body weight loss is necessary to improve hepatic steatosis, but > 7% weight loss is required for histological improvement in NASH and fibrosis

NASH with significant fibrosis (fibrosis stage ≥2 or fibroscan value > 10.51)

↓

Lifestyle modifications
Plus
Physical exercise
Plus
One or more of the following medications:
1. Pioglitazone:
   - Indicated in biopsy-proven NASH patients with and without type 2 diabetes mellitus
   - 15-30mg daily dose of Pioglitazone is recommended
   - Treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy and in patients with normal ALT at baseline, no recommendations can be made
2. Vitamin E:
   - Vitamin E may be considered at a daily dose of 800 IU/day in nondiabetic adults with biopsy-proven NASH
3. Ursodeoxycholic acid (UDCA):
   - According to NICE, EASL, Asia-pacific and AASLD guidelines, UDCA is not recommended for treatment of NAFLD, NASH or hepatic fibrosis
   - But few recent studies showed (1) (Parikh P et al (2016) UDCA is an effective and safe alternative to Vitamin E in nondiabetic–non-cirrhotic Indian NAFLD patients

   (2) (Mappala H, 2019) UDCA is a frontline therapeutic option for NASH and thereby preventing its progression to cirrhosis and liver cancer
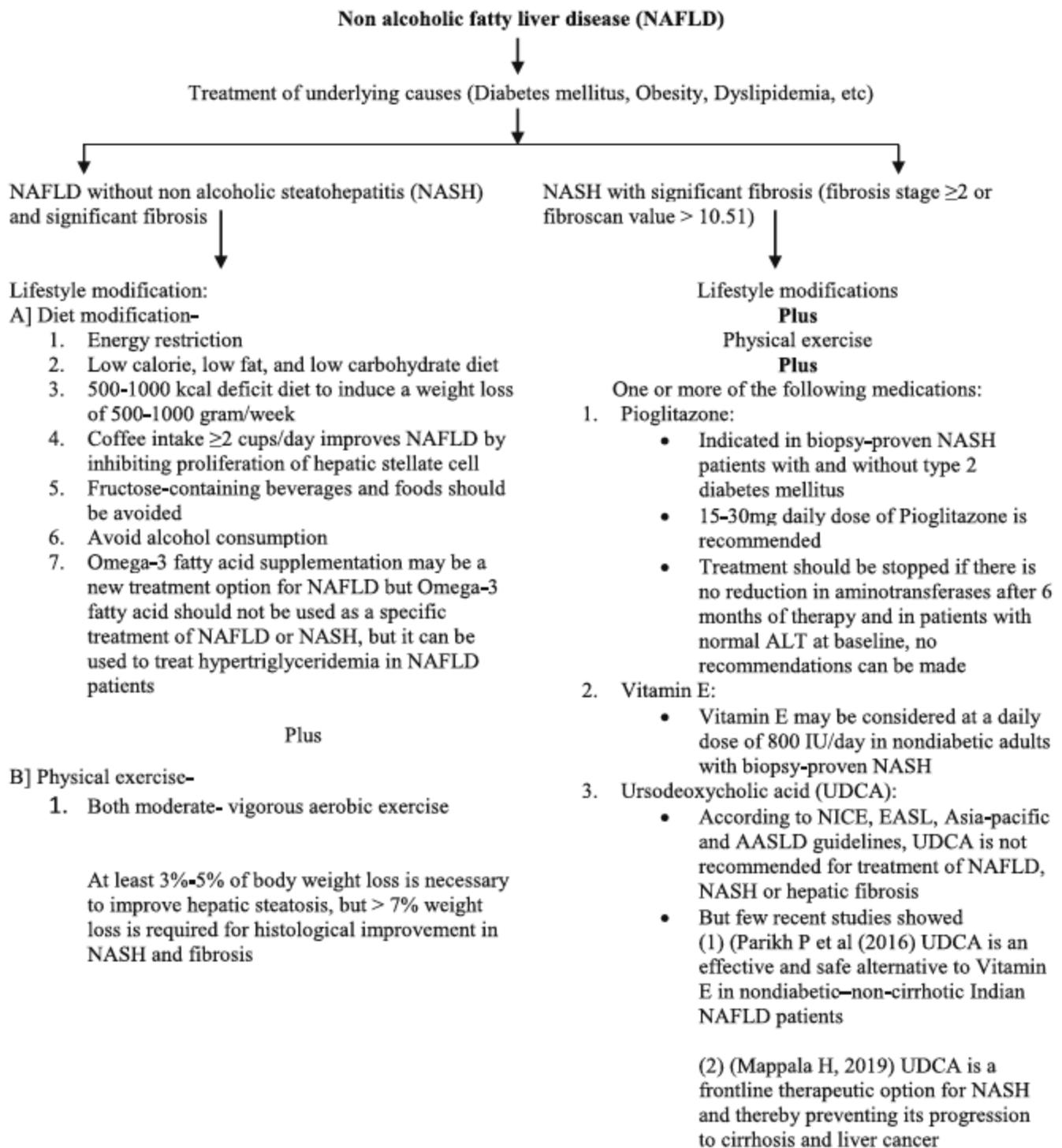
Fig. 3. Algorithm of lifestyle modification and pharmacology in NAFLD patients [35].

Salomone *et al.* stated that fructose-containing foods should be avoided because it may appear as one major factor for initiation of hepatic steatosis and its progression to NASH and more severe liver fibrosis stages [33]. Other options of management NAFLD by Marchesini *et al.* explained that physical exercise could be considered in both moderate and vigorous aerobic exercise, such as walking and stationary cycling. Resistance training (150-200 minute/week in 5 sessions) effectively reduces hepatic steatosis by decreasing body weight. However, any choice of exercise should be based on the patient's preference [34]. Chalasani *et al.* reported that generally, 5-10% reduction of body weight in obese patients over 6 to 12 months had been achieved through diet modification and physical exercise. At least 5% of body weight loss is necessary to improve liver organ [1]. Therefore, the NAFLD first-line management is lifestyle modification, including 7-10% weight loss by combining energy restriction strategies with the deterrence of high fructose and saturated fat in foods, consumption of omega-3 fatty acid supplement, and moderate to vigorous physical exercise [34]. When failed, clinicians may consider adding pharmacotherapy, especially when biopsy is proven by the severity of NASH and fibrosis at stage ≥ 2 or fibro scan value more than 10.51 (Fig. 3) [29], [34].
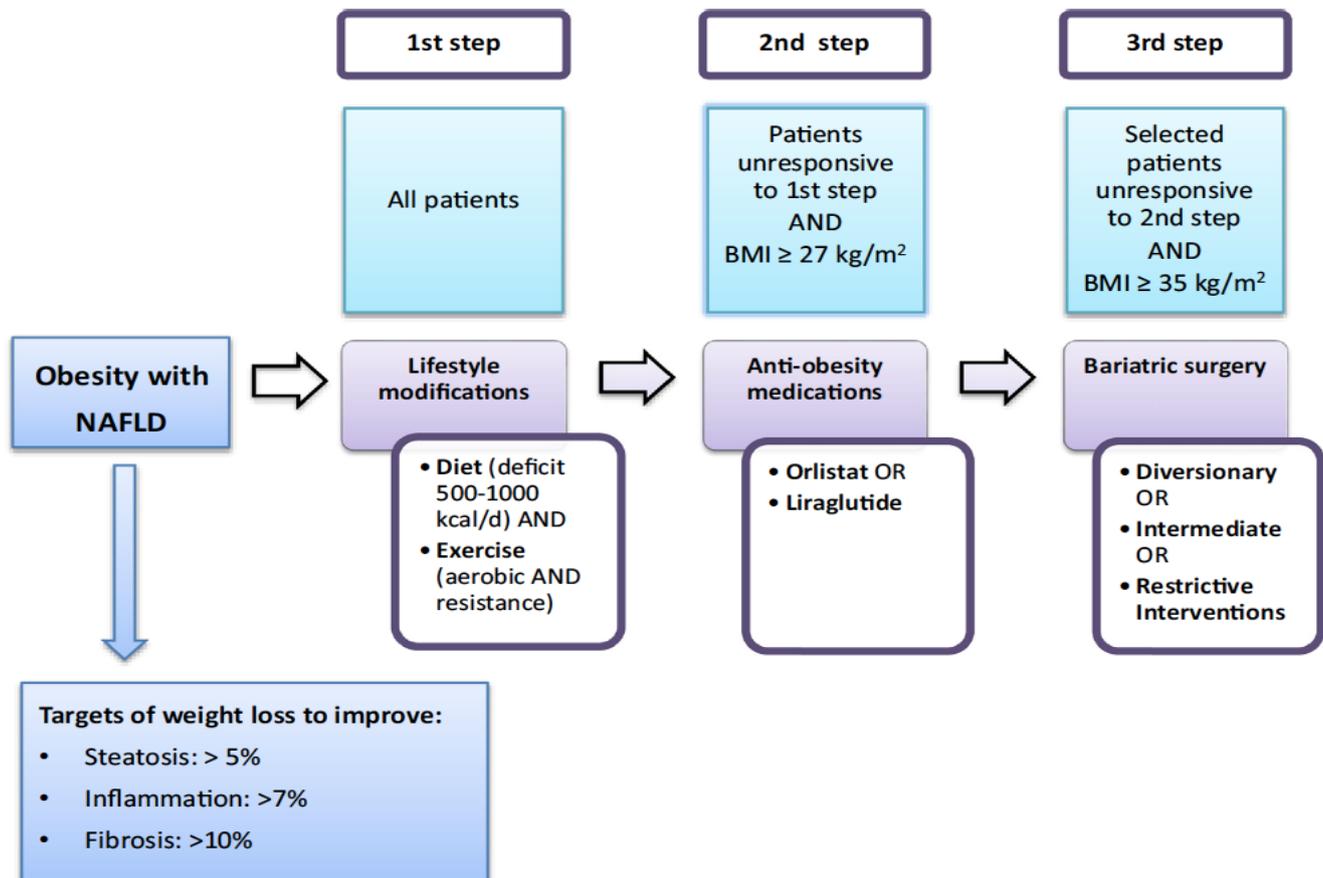
Fig. 4. Obesity-related algorithm for the therapeutics of NAFLD patients [36].

TABLE II: RECOMMENDED NUTRITIONAL MANAGEMENT FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN OBESE PATIENTS [37]

No	Dietary Options	Recommended Dietaries	Not Recommended Dietaries
1	Calories restriction (500-1000 kcal/d deficit): low fat (<30%) or low CHO (<40%)	* Vegetables (3-5 servings/d)	* Fast food (least possible)
2	If the low-CHO diet is decided, use more PUFA, MUFA, and proteins derived from fish, poultry, nuts, and legumes.	* Legumes (4 servings/ wk) * Fruits (2-4 servings/d) * Whole grains (daily)	* Empty calories (cakes, cookies, ice cream, candies)
3	If the low-fat diet is decided, use more low-GI foods and proteins derived from fish, poultry, nuts, and legumes.	* Nuts (4 servings/wk) * Olive oil	* Unprocessed red meats (>300 g/wk) * Processed meats (>2/wk)
4	Reduce consumption of trans FA (<1%), saturated fats (<7%), and cholesterol (<200 mg/d)	* Oily fish (tuna, salmon, and sardines) (100 gr serving at least 2 / wk)	* Potato chips (least possible) * Potatoes
5	Increase intake of cereal-derived non-soluble fiber (wholegrain) (25 g/d)	* Low-fat dairy products	* Sugar-sweetened beverages (least possible) * Salt

CHO: Carbohydrate; GI: Glycemic Index; MUFA: Monosaturated fatty acids; PUFA: Polysaturated fatty acids.

Some studies have recommended that some stepwise approaches also seem appropriate for the bodyweight management in obese patients with or without NAFLD [36]. At the first step, the exercise and diet are more recommended. When the first step fails, the addition of pharmacotherapy is recommended in patients with body mass index (BMI) ≥ 30 kg/m^2 or those ≥ 27 kg/m^2 with obesity-related comorbidities.

When the second step also fails, bariatric surgery should be considered in selected patients with BMI ≥ 40 kg/m^2 or those with BMI ≥ 35 kg/m^2 with obesity-related comorbidities [30]-[34]. Respectively, even lower BMI for the Asian population with NAFLD (BMI 32.5 kg/m^2) has also been recommended as cut off for bariatric surgery by the Asia-Pacific Working Party (APWP). A summary of these management steps is presented in Fig. 4. An overview of recommendations and specific food groups that should be promoted in NAFLD patients is also provided in Table 2.

Additionally, some studies have reported that vitamin D can be considered as adjuvant therapy. Numerous researches discovered that vitamin D has a role as an antioxidant with lipoprotective and anti fibrogenic effect by reducing secretion of TGF-β from primary hepatic stellate cells. However, it also depends on the vitamin D receptor genotype and the vitamin D receptor levels [52], [53]. Randomized control trial study from Amiri *et al*. showed that vitamin D supplementation combined with a weight loss diet revealed no significant effect on anthropometric examination. The authors concluded that vitamin D therapy might show a positive result on liver enzyme and lipid profile [54]. Many studies are currently established to invent other drug agents as targeted therapy or adjuvant therapy, but the evidences have not been strong enough. Further researches are needed for NAFLD management based on pathogenesis and progressivity disease. There are some approved anti-obesity medications for NAFLD patients include orlistat and liraglutide as glucagon-like peptide (GLP-1 analog), insulin-sensitizing agent, thiazolidinediones agents, ursodeoxycholic acid, vitamin E, and statin agents (Table 3) [38]-[41].

TABLE III: EVIDENCE-BASED RECOMMENDATION OF PHARMACOLOGY AGENTS

Agent	Studies	Recommendations
Orlistat (enteric lipase inhibitor)	Ziegler-Sagi *et al.* [38] Harrison *et al.* [39]	Ziegler-Sagi *et al.* reported in two randomized controlled trials and concluded that orlistat is able to improve ALT and steatosis, but its effect on liver histology could not be evaluated. Harrison *et al.* also concluded that orlistat did not improve body weight or liver histology.
Metformin (insulin-sensitizing agents)	Uygun *et al.* [40]	Metformin is known to have no significant effect on the histological structure of the liver, so its use is not recommended as a specific treatment for liver disease among adults with NASH.
Pioglitazone (thiazolidinediones)	Belfort R *et al.* [41] Sanyal *et al.* [42] Lincoff *et al.* [43]	Pioglitazone can be considered to treat steatohepatitis in patients with biopsy-proven NASH.
Vitamin E (α-tocopherol)	Harrison *et al.* [44] Sanyal *et al.* [45]	Oral preparation of vitamin E at a regular daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH. Therefore, it should be considered as a first-line pharmacology for NAFLD or NASH.
UDCA, omega-3 fatty acids	Klein *et al.* [46] Leuhner *et al.* [47] Ratziu *et al.* [48] Spadaro *et al.* [49]	UDCA is not recommended for NAFLD or NASH patients. Sometimes, it is premature to recommend omega-3 fatty acids for the specific treatment of NAFLD or NASH. Still, these agents may be considered as the first-line agents to treat hypertriglyceridemia in NAFLD patients. Spadaro *et al.* stated that supplementation of omega-3 fatty acids 2 gr/day for six months might decrease triglyceride, steatosis, and ALT level.
Statin agents	Lewis *et al.* [50] Nelson *et al.* [51]	Lack of evidence shows that NAFLD patients and NASH are at increased risk for serious drug-induced liver injury from statin. Statin can be used to treat dyslipidemia in NAFLD patients or NASH.

UDCA: Ursodeoxycholic acid; ALT: Alanine aminotransferase.

VI. CONCLUSION

Obesity has been significantly associated with the escalating number and severity of NAFLD. It is initiated by the accumulation of TG within the hepatocytes cells, which is also influenced by the presence of adipocytokine secretion and leptin. Individuals with risk factors for metabolic syndrome disorders and insulin resistance can increase NAFLD progression to NASH. Exposure to lipids and excess carbohydrates causes the lipotoxicity and glucotoxicity to the hepatocyte cells. Throughout the mechanisms of mitochondrial defects, endoplasmic reticulum stress, and oxidative stress, obese individuals are capable of undergoing a complex inflammatory process in the liver, associated with the development of NAFLD and NASH. Accordingly, several multilevel management approaches with the primary objective of targeting obesity have been suggested, especially concerning NAFLD treatment. They include lifestyle changes through dietary and intake restrictions, physical activity, as well as the consumption of evidence-based lipoprotective agents, such as coffee and supplementation of omega-3 fatty acids. Other management options include anti-obesity drugs and bariatric surgery, which is proven to be effective if lifestyle modification methods have not provided maximum therapeutic results.

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