Fatty Liver Disease: Diagnosis and Treatment

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The liver is the body's largest organ and is essential for maintaining the body's balance. Therefore, it is a vital organ for life, as it is responsible for the entire body's metabolism and participates in a variety of crucial physiological processes.[1-3] The breakdown of xenobiotic compounds, the realization of gluconeogenic reactions, the production of bile, the oxidation of lipids, the supply of energy for the continuation of physiological processes, the detoxification, digestion, and metabolism of the blood. In addition, the metabolism of amino acids and the removal of nitrogenous wastes are all handled by this organ. It also plays a crucial function in metabolism, protein synthesis, and amino acid metabolism.[4-6] Viral hepatitis, alcohol consumption, sedentary life, hepatic fat accumulation of 5% or more, drug-induced liver disease, autoimmune liver disease, obesity, Type 2 diabetes, and metabolic syndromes, such as high-fat diet, corn syrup, high-fructose foods, and pizza excessive use of quick meals and sugary drinks cause fatty liver.[7-12] There are two main types of fatty liver disease: alcoholic liver

ABSTRACT

The liver is the largest organ of our body, which plays a role in the physiological process in the body and is most exposed to toxins. The liver's functions are essential for life since it is involved in macronutrient metabolism. Fatty diets, excessive alcohol consumption, sedentary lifestyles, ready-made foods and beverages, and fructose metabolism in the liver are all factors that contribute to liver fat. In the advanced stage of fatty liver, changes in liver cells, cirrhosis, and hepatocellular carcinoma, which rank first in the world in terms of mortality, are seen. Therefore, current treatments and future approaches to fatty liver research are of tremendous interest. The results of investigations looking into the causes and current treatments for alcoholic liver disease and non-alcoholic fatty liver disease were compiled in this review.

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disease (ALD) and non-alcoholic fatty liver disease (NAFLD). The hepatic portal vein transports the majority of the blood to the liver from the spleen and gastrointestinal system. This venous blood contains antigens that are then exposed to the immune repertory of the liver, these antigens establishing the liver as a critical immunological site for both immune tolerance and activation. Irregular immunological processes can affect both the liver and systemic immune responses. Kupffer cells, mucosal-associated invariant T (MAIT) cells, αβ T cells, lymphoid cells (ILCs), γδ T cells, natural killer T (NKT) cells, and natural killer (NK) cells all reside in liver B cells.[4,13] NK cells make up 40% of the total lymphocytes in the human liver.[4,14] This result shows that NK cells have an important potential in the regulation of immunity in the liver.[4] Depending on the type of liver damage and the underlying causes, immune reactions are affected by a variety of mechanisms.[15,16] Chronic inflammation has been indicated as an important trigger of liver fibrogenesis.[17]

FATTY LIVER AND INFLAMMATION

Various defense systems have evolved in living things in response to attacks on cells and tissues. Inflammation is defined as a physiological response to tissue damage when the organism is exposed to biological, physical, or chemical factors.[18,19] Cytokines are cellular regulatory proteins. Special cells (T lymphocytes) release them in response to specific stimuli, and they influence the behavior of targeted cells. The effects of cytokines might be systemic or local. Although different cells in different tissues secrete the same cytotoxin, it has the same biological function.[20] Kupffer cells generate a considerable amount of inflammatory factors when the liver is wounded. To treat and prevent liver damage induced by alcohol intake, it is vital to limit the liver's inflammatory response.[21] Metabolic syndrome studies have reported that patients have increased inflammation, which facilitates the development of fatty liver, and increases the value of some inflammatory mediators, including tumor necrosis factor-alpha (TNF-α) and lipid peroxidase, in fatty liver.[22,23] In the pathogenesis of ALD and NAFLD, a high number of inflammatory cells and inflammatory mediators play both useful and destructive roles in the liver. It causes hepatocyte destruction and liver fibrosis, for example, while also accelerating liver regeneration and protecting the liver from bacterial infections. Inflammation generated by low bacterial infection causes liver damage at both the ALD and the NAFLD, where liver regeneration is not required due to mild harm.[24] Another inflammatory cytokine, interleukin-22 (IL-22), promotes liver regeneration, whereas interleukin-17 (IL-17) induces liver injury. In response, the expression profiles of antagonistic cytokines shift towards IL-17 in the advanced stage.[25] Cytokines also have an important role in the development of NAFLD.[26] TNF-α is an inflammatory cytokine produced by a variety of cells, including macrophages and kupffer cells in the liver. TNF-α is a crucial factor in the development of inflammation and insulin resistance.[27]

ALCOHOLIC LIVER DISEASE

Alcoholic liver disease is a term used to describe liver disease caused by excessive alcohol use. Lipoatrophy starts with fat buildup in the liver and can progress to severe alcoholic steatohepatitis.[28] When they are detected early and their alcohol use is minimized, some persons may be recycled.[29]

Ethanol (EtOH) is produced by the enzymatic action of brewer's yeast on sugar-containing compounds during fermentation or distillation.[30] GABAergic neurotransmission is harmed by long-term use of EtOH. Oxidative stress, astrocytic dysfunction, neuroinflammation, and neurotoxicity are all caused by chronic EtOH exposure.[31] The stomach absorbs 20% of ethanol quickly, whereas the duodenum absorbs the remaining 80%.[32,33] Because ingested alcohol dissolves quickly in water, it enters the bloodstream and is transported to the tissues immediately. Alcohol, which is easily swallowed and passes through the mucosal epithelium, begins to be absorbed before it reaches the stomach due to its short-chain chemical structure. The rate of alcohol absorption is inversely related to stomach fullness and directly proportional to the rate of alcohol consumption. While only 5-8% of the alcohol consumed by the circulatory system is expelled from the body without being processed through respiration, urine, or perspiration, enters 90% is destruction process in the liver.[30] In the liver, there are two phases to the breakdown of alcohol. The oxidation of ethanol to acetaldehyde and the conversion of acetaldehyde to acetic acid are the two stages involved. In oxidation, both the alcohol dehydrogenase route and the microsomal ethanol oxidation system are involved. The microsomal ethanol-oxidizing system (MEOS) or the cytochrome P450 family 2 subfamily E member 1 (CYP2E1) enzymes are both involved. Alcohol dehydrogenase is a zinc-containing cytosolic enzyme found in the cytoplasm of liver cells. Almost all of the conversion takes place through this pathway when a low dose of alcohol is consumed. The liver's NAD+ capacity restricts the rate of breakdown to 8-10 g ethanol/hour. Hunger and a low-protein diet slow the breakdown of alcohol. The CYP2E1 enzyme is present in the endoplasmic reticulum of the liver. Because the enzyme's activity is 4-40 times lower than that of alcohol dehydrogenase, it has no importance on the breakdown of alcohol in modest or moderate quantities. When the liver's NAD+ capacity is exceeded (one promille = alcohol level greater than 100 mg/dl), it becomes increasingly significant. Regular use of alcohol activates the CYP2E1 enzyme. (enzyme efficacy may increase up to ten times). Increased enzyme content accelerates the deterioration rate of alcohol and decreases blood levels.[34,35] Most of the acetaldehyde is oxidized by the acetaldehyde dehydrogenase 2 (ALDH2) variant.[36] Slow inactivator individuals who are homozygous or heterozygous for low activity have an acetaldehyde response, which causes consequences like blushing even when eaten in little doses. These people are more numerous in

East Asian races and have a lower risk of ALD.[37] It is defined in American dietary guidelines as "one drink containing approximately 14 g of alcohol". This ratio corresponds to approximately 150 ml of wine (12-13% weight/volume), 350 ml of beer (5% weight/volume), or 40-45 ml of liqueur (40-45% weight/volume).[38]

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines alcohol use disorder as more than two drinks per day for women and more than three drinks per day for men, while excess alcohol intake is specified as four for women and more than five for men within two hours.[39] Individuals with an alcohol use disorder may be diagnosed with alcoholic fatty liver disease (AFLD). Alcohol-induced liver steatosis, which is generally seen in the form of macrovesicular steatosis, is seen in approximately 90% of individuals with high alcohol consumption and may develop within two weeks after continuous and heavy alcohol consumption. If alcohol is completely abandoned, improvements in lipolysis are observed.[40]

NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease is now known as metabolic dysfunction-associated fatty liver disease (MAFLD).[41,42] It is stated that the disease affects approximately one-quarter of the world population and it is associated with significant morbidity and mortality.[42-44] A recent study predicts that NAFLD-related liver diseases will increase from 64% to 156% worldwide by 2030.[45] Obese people have a rate of 90%, Type 2 diabetics have a rate of 76%, and non-overweight people have a rate of 16%.[46,47] In the coming years, NAFLD is projected to become a prominent cause of liver transplantation.[48]

The course of the disease varies from fatty steatosis to non-alcoholic steatohepatitis (NASH).[49] 5-8% of patients who develop NASH may develop cirrhosis of the liver within five years.[50] Within three years, 12.8% of patients with liver cirrhosis develop hepatocellular carcinoma (HCC).[51] In 70% of NASH patients, metabolic syndrome and its components have NAFLD risk factors, including sedentary lifestyle and increased fat in the diet, thus considered a major cause of cryptogenic cirrhosis.[52,53]

Cardiovascular disease, chronic renal disease, insulin resistance, obesity, type 2 diabetes, postoperative difficulties after major liver surgery, and an increased risk of colorectal cancer are all linked to NAFLD.[54-56] The prevalence of NAFLD is also affected by gender, age, sleep apnea, ethnicity, and the presence of endocrine disorders (hypopituitarism, hypothyroidism, polycystic ovary syndrome, and hypogonadism).[57,58]

METABOLIC EFFECTS OF FRUCTOSE

Examining glucose metabolism will help understand the influence of fructose on fatty liver metabolism. Glucose is metabolized by glucokinase and hexokinase. Fructokinase is the enzyme that mainly breaks down fructose. Fructokinase uses adenosine triphosphate (ATP) to phosphorylate fructose to fructose-1-phosphate. Aldolase B, D-glyceraldehyde, and dihydroxyacetone phosphate are all produced. Fructose metabolism resembles glucose metabolism at this point. Glycogen and triglycerides are formed when glucose is consumed.[59] As can be seen, the first two enzymatic processes differ significantly between fructose and glucose metabolism. The liver is the primary site for fructose metabolism.[60] Fructose is different from glucose in that it can generate carbohydrate metabolites without triggering the hepatic insulin response.[61,62] In the liver, the major isoforms of fructose are ATP and intracellular phosphate.[63-66] The purine nucleotide cycle, which leads to the synthesis of uric acid, is triggered by a drop in intracellular phosphate, which activates the enzyme AMP deaminase, which converts adenosine monophosphate (AMP) to inosine monophosphate (IMP).[67] Fructose also stimulates uric acid synthesis from the amino acid precursors.[68-70] Fructose's ability to induce ATP consumption has been shown in both intravenous and human populations.[63,71] Uric acid levels rise when you consume fructose.[72,73]

Therefore, the unique thing about fructose in glucose is that it causes a temporary decrease in intracellular phosphate and ATP levels when fructose is metabolized, associated with nucleotide cycle and uric acid production. The decrease in ATP level, a disruption in protein synthesis, induction of oxidative stress, and the emergence of an important role in its fructose-mediated effects may cause its appearance by causing a number of manifestations, including mitochondrial dysfunction.[63,74] As a result of studies, the consumption of fructose has been reported to stimulate lipogenesis in animals as well and to block the oxidation of hepatic β-fatty acid.[75,76] Similarly, studies seen in humans have demonstrated that fructose intake stimulates de novo lipogenesis and prevents the oxidation of fatty acids in the liver.[76,77,78] All of these factors present fructose as sugar that causes fatty liver.

TREATMENT OPTIONS FOR FATTY LIVER

A. Treatment Methods for Alcoholic Fatty Liver Disease

The therapy of AFLD is divided into two parts: traditional treatment, new therapeutic options, and novel potential treatments

Traditional Treatment Methods:

Liver Transplantation

Liver transplantation (LT) is one of the most successful treatments for a variety of acute and chronic liver diseases, and it is one of the approaches that has lately modified the natural course of liver disease.[79,80] According to the studies, 70 nations reported 35784 liver transplants to the Global Observatory on Donation and Transplantation in 2019.[79,81]Although LT enhances the quality of life and length of life, it also carries a number of risks, including the spread of disease from the donor to the recipient.[79,82,83] Patients with severe alcoholic hepatitis related to ALD who do not react to steroids may consider LT as a last resort. Patients should abstain from alcohol for six months and receive adequate addiction therapy before undergoing liver transplantation, according to health institutes.[84] While one study suggested that a six-month abstinence period would allow the liver to heal with medical treatment and possibly not require transplantation,[85] another study noted that some improvement in liver function may occur within three months of abstinence, and many patients may die after 6 months of waiting.[86] While the three-month mortality rate is 70%, if transplantation is not performed, the mortality rate rises to 90% or more.[87,88] It is concerning because of the possibility of recurrence among patients.[89] The 10% to 50% recurrence rate after transplantation is a big issue.[90,91] However, liver transplantation due to ALD is associated with a high incidence of cardiovascular complications.[92] LT remains the only curative treatment for decompensated NAFLD cirrhosis with or without HCC.[93]

Treatment and Deprivation for Alcohol Addiction

One of the most significant processes in the treatment of ALD is limiting alcohol use, which also has an impact on death rates. The seven-year survival rate for patients who stopped alcohol was 80%, while the seven-year survival rate for those who continued to drink alcohol dropped to 50%.[94] Drugs used to treat addiction, such as naltrexone and acamprosate,

have been observed to lower alcohol intake in high alcohol consumption patients,[95,96] and symptoms of topiramate withdrawal in addicts.[97]

Disulfiram, an acetaldehyde dehydrogenase inhibitor, is used to reduce alcohol intake because it causes serum acetaldehyde accumulation that causes nausea, vomiting, abdominal pain, and dizziness.[98] A γ-amino butyric acid agonist, baclofen has been found to be effective in promoting deprivation.[99] In one study, while taking 10 mg of baclofen twice a day, the daily number of beverages reduced by 68%, while when taking 20 mg of baclofen, the daily number of beverages was reduced by 53%.[100] Drugs such as naltrexone and disulfiram help maintain deprivation, and they should be avoided in patients with liver problems since they cause problems such as hepatotoxicity.[101] However, the use of acamprosate, topiramate, and baclofen in such patients is not considered objectionable.[99,102,103] Another drug used to maintain abstinence is metadoxine (MTDX). MTDX is readily absorbed and boosts acetaldehyde dehydrogenase activity when taken orally, in addition to aiding abstinence. Thus, it contributes to acute ethanol intoxication by increasing alcohol metabolism. Thus, it plays a role in acute ethanol intoxication by causing an increase in alcohol metabolism.[103] Improvement in liver function tests was observed in as little as one month after using MTDX in research of alcoholic liver patients.[104] While 74.5% of MTDX users continued their abstinence, non-users were determined to have a rate of 59.4%.[105] Most European countries utilize this medicine, which is not used in the United States.

Food and Nutritional Support

Patients with advanced ALD eat insufficiently due to several factors, including malnutrition, anorexia, and encephalopathy, with the severity often associated with this malnutrition.[94,106] Protein and energy requirements are rising in alcoholic liver patients as a result of disease stress and poor nutrition. The American College of Gastroenterology (ACG) and The American Association for the Study of Liver Diseases (AASLD) recommend 1.2 to 1.5 g/kg of protein per day and 35 to 40 kcal/kg of calories per day for energy intake in patients with ALD.[107] The most effective way to supply this amount of calories is through enteral methods. Because enteral feeding has been shown to minimize complications and improve one-year mortality in patients in important research.[108,109] In patients in coma, parenteral nutritional support may be necessary. The amounts of vitamins (folate, vitamin B6, vitamin

B12,[110,111] vitamin A, and thiamine[112]) and minerals (selenium, zinc, copper, and magnesium) in ALD are thought to vary, and these variations may have an impact on liver disease.[113] It has been observed that zinc levels decrease especially in ALD patients and animal models, and it has been shown that ALD improvement occurs as a result of supplementation of this mineral.[114]

Corticosteroids and Glucocorticosteroids

Infection is one of the most common causes of death in patients with alcoholic hepatitis. Factors such as malnutrition and medical procedures increase the risk of infection. Hepatitis C virus (HCV) promotes liver damage and the development of HCC, making it a risk factor for ALD progression.[115,116] This effect occurs when both alcohol and HCV cause a change in cellular immunity, increasing free radical oxidative damage and causing the HCV to self-replicate if exposed to alcohol. Therefore, the occurrence of an infection along with the disease reduces the chance of survival.[117,118] Alcoholic patients with HCV infection have a 30-fold increased risk of cirrhosis and a two to eight-fold increased risk of death when compared to those who do not have HCV infection.[119,120] Based on this information, HCV screening should be screened for all ALD patients before treatment begins and all HCV patients should be advised to restrict their alcohol consumption.[121]

Corticosteroids have potent anti-inflammatory properties and are useful in the treatment of autoimmune hepatitis. To date, many different clinical investigations on the use of corticosteroids to treat individuals with ALD have been undertaken.[122-124] While it can be said that the use of corticosteroids is beneficial, although not valid for all patients, 40% of the patients do not respond to corticosteroids.[125] In a meta-analysis combining data from 3 randomized control studies, it was found that when suitable patients were treated with 40 mg/day prednisolone (a synthetic corticosteroid) for 28 days, the survival rate in the placebo was 85%, compared with 65 % for patients on glucocorticosteroid, while the death rate dropped from 35% to 15% for steroids.[124] Although some patients have a beneficial effect by responding partially to steroid treatment, it has been observed that patients have not responded. It is recommended to stop steroid therapy in patients who do not respond.[126] Steroids are usually avoided in patients with active infection, gastrointestinal bleeding, chronic hepatitis B virus infection, or hepatorenal syndrome (HRS).[127] Therefore, such patients can be treated with pentoxifylline (PTX) as a second line.[128]

New Therapeutic Options and Novel Potential Treatments:

S-Adenosylmethionine

S-adenosylmethionine (SAM) is a methyl donor involved in many methylation reactions critical to normal liver function. SAM levels have been reported to be below in ALD patients. Therefore, raising SAM levels is thought to be a potential therapy. Various animal studies have seen that preventing a decline in SAM levels can prevent liver injury.[129]

Various Chemokines and Interleukins

Chemokines play a key role in the pathogenesis of alcoholic hepatitis. Many distinct chemokines, such as CXCL5, CXCL6, CXCL10, and CCL20, have been found to be highly elevated in the ASH liver compared to normal liver levels in studies.[130,131] Interleukin-8 (IL-8) is one of the most prominent neutrophil chemoattractants, and high IL-8 levels are associated with the severity of alcoholic hepatitis.[130] IL-22, a member of the interleukin-10 (IL-10) family that inhibits the production of proinflammatory cytokines, is implicated in bacterial infections and tissue repair.[132] IL-22 contains anti-steatotic and antioxidant properties, and it could be used to treat ALD patients. Also, auxiliary T cell levels involved in IL-22 production are found to be associated with improvement in alcoholic hepatitis patients.[133] In ethanol-fed mice, administration of recombinant IL-22 has improved the condition,[134] whereas blocking the IL-22 receptor has worsened the condition.[135]

Endocannabinoids Antagonists

In experiments on animal models of alcoholic liver injury, researchers are determined that mice lacking cannabinoid receptor type 1 (CB1) are resistant to fatty liver damage, but mice lacking cannabinoid receptor type 2 (CB2) are more susceptible.[136,137]

Osteopontin Inhibition

Osteopontin (OPN), an extracellular matrix protein, is involved in wound healing in response to injury in many organs.[138] Another study observed that mice without OPN had weakened due to alcohol-induced liver disease.[139]

B. Treatments of Non-Alcoholic Fatty Liver Disease

Although NAFLD treatment methods have common points with AFLD treatment methods, they differ in some ways.

Lifestyle Change

A lifestyle change aimed at increasing weight loss and physical activity is critical for those with NAFLD. It is possible that patients will be advised to lose 10% or more of their body weight. This state is associated with an improved cardiovascular risk profile and steatosis in the patients.[140] Hepatic inflammation and a reduction in hepatocellular damage can be seen even with a 7-9% weight loss.[141,142] In studies, patients who got dietary treatment and engaged in moderate physical activity for 200 minutes per week for 48 weeks had less steatosis and inflammation in their liver biopsy, as well as a decrease in body weight.[141]

Diet

Patients should follow a calorie-restricted diet targeted at losing 0.5-1 kg/week until reaching their target weight.[143] It is suggested that as the diet advice avoid saturated fats, simple carbohydrates, and sugary drinks.[144,145] Recently, there has been an increase in interest in omega-3 (ω-3) polyunsaturated fatty acids (n-3 PUFAs) in the diet. Studies show that NAFLD patients consume less n-3 PUFA.[146,147] In studies a reduction in liver fat with n-3 PUFA supplementation was, but no significant reduction in ALT (Alanine aminotransferase) levels.[148] Adding fish oil to the diet may offer treatment options for patients. Dietitian intervention is also important for these patients. Lifestyle changes in dietitian control may be preferred in terms of observing improvement in weight loss NAFLD.[149]

Exercise

Aerobic exercise improves skeletal muscle insulin sensitivity and lowers insulin resistance, which is one of the important mechanisms that lead to NAFLD.[150,151] Studies examining moderate-violence, high-violence, and resistance exercise have associated improvements in liver enzymes and a reduction in steatosis, independent of weight loss.[152-154] Individuals with NAFLD should be advised to increase physical activity. There are some approaches that propose 30 minutes of moderate exercise five times a week.[155] It has been observed that individuals with NAFLD are less active than healthy individuals.[156,157] There are studies showing that they do not exercise much and are less ready for lifestyle changes.[158,159]

Bariatric Surgery

Bariatric surgery is becoming important in the treatment of obese patients with NAFLD. Weight loss from bariatric surgery increases insulin sensitivity and has specific effects on liver histology.[160] However, it is not recommended as first-line therapy because of the lack of long-term effect data and the risk of postoperative hepatic failure.[161,162] In adults with a body mass index (BMI) > 50, surgery may be considered the first treatment.[143]

Vitamin E

Experiments with vitamin E have been linked to improved liver function and lower levels of oxidative stress indicators. However, improvement in the disease's histology grading is less substantial.[163,164] In another study, it was observed that vitamin E was associated with a decrease in steatohepatitis in the childhood NASH study.[165] A study observed that people who took vitamins E and C for six months were no better than those who took a placebo in treating NASH.[166] Six-month research comparing the combination of pioglitazone and vitamin E to vitamin E alone observed that both groups had lower serum ALT levels, but the combination group had a significant histological improvement.[167] According to meta-analysis research, high-dose vitamin E supplementation (>400 IU/day) is linked to an increase in all-cause mortality and cardiovascular fatalities, reversing the trend toward vitamin E therapy.[168]

Pentoxifylline

Pentoxifylline inhibits proinflammatory cytokines, including TNF-α. In vitro studies on hepatic stellate cells (HSC) are observed anti-fibrogenic effects.[169,170] Following a one-year treatment with PTX, researchers found two percentage point reduction in NAFLD activity in patients. In addition, steatosis, inflammation, and fibrosis were also produced significant improvements using PTX.[171] However, a randomized, multicenter double-blind research undertaken in 65 institutions in the United Kingdom with over 1,000 patients indicated that PTX had no effect on survival or disease progression in patients with severe NASH.[172,173]

Metformin

Metformin is preferred in the first stage because it improves insulin sensitivity and is an agent for type 2 diabetes mellitus (T2DM). Widely tested in NAFLD. This is because insulin resistance is an important pathogenic feature of T2DM patients. Studies with metformin have shown that there may be a histological benefit.[174,175] However, other randomized controlled studies have yielded negative results.[176,177] In other meta-analysis studies, it was also found that Metformin had no therapeutic effects on liver histology in NASH and NAFLD patients.[178,179]

Angiotensin Receptor Blockers

Non-alcoholic fatty liver disease is associated with metabolic syndrome and hypertension is a major component of metabolic syndrome. Therefore, Angiotensin receptor blockers may be part of the NAFLD treatment. A study in NAFLD patients was observed that losartan (angiotensin II receptor antagonist) treatment was associated with improvement in necro-inflammation and fibrosis.[180]

Agents to Lower Lipids

Studies have shown that gemfibrozil is associated with an improvement in lower levels in NAFLD patients compared to placebo.[181] Clofibrate, on the other hand, had no beneficial effect on liver tests or histology scores.[182] In investigations, ezetimibe (an inhibitor of intestinal lipid reabsorption) decreased blood TNF-α, hepatic lipid content, and ALT levels in NAFLD mice.[183,184]

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA) is a naturally-occurring bile acid commonly used mostly for chronic cholestatic liver disease.[185] UDCA reduces oxidative stress. It has been explained by studies that it has various anti-apoptotic, antioxidant, and anti-inflammatory properties.[186-189] In studies are observed that UDCA improves liver enzymes and hepatic steatosis in patients with NAFLD.[190,191]

Anti-Obesity Drugs

Non-alcoholic fatty liver disease is exacerbated by obesity. Therefore, anti-obesity medications and pharmacological agents can be evaluated as viable candidates for controlling and treating the disease process. However, data on the efficiency of anti-obesity medicines other than orlistat in the treatment of NAFLD are scarce.[192]

Orlistat

Orlistat is an anti-obesity drug that inhibits fat absorption. A study showed an improving effect on liver enzymes in NAFLD patients but had no effect on liver fibrosis score.[193] In another study, the effect of orlistat on NAFLD was evaluated in patients who received a 1400 kcal diet and vitamin E (800 IU) per day. Orlistat (120 mg three times daily) did not increase weight loss or improve liver enzymes and histopathology in 50 overweight subjects when given.[194]

Lorcaserin

Lorcaserin is a serotonin 2C receptor agonist that improves T2DM and promotes weight loss. In a six-month, randomized, placebo-controlled double-blind study, lorcaserin reduced the fatty liver index in 48 patients without T2DM.[195]

Probiotics

Intestinal bacterial overgrowth increased intestinal permeability, and increased paracellular leakage of intestinal luminal antigens are all variables that promote the development of NASH in patients with NAFLD, just as they are in individuals with AFLD. As a way, probiotics could be a viable treatment option for NASH patients.[196,197] There has been improvement in liver enzymes relative to placebo in NAFLD patients who were treated in a randomized controlled trial using Streptococcus thermophilus and Lactobacillus bulgaricus.[198] In another randomization study, a significant reduction in steatosis, TNF-α, AST, and NASH was observed in the combination treatment group, with patients receiving Bifidobacterium longum in combination with fructooligosaccharides, within the lifestyle modification group alone, and lifestyle modification (exercise and diet).[199]

Liver Transplantation

Since the increasing prevalence of NAFLD, liver transplantation is an increasing treatment modality for NASH cirrhosis.[200] In a study in which liver transplantation was performed in 98 patients for NASH cirrhosis, recurring steatosis was observed in 70% of the patients, and NASH was observed in 25% of the patients. However, none of the patients developed graft failure or required retransplantation[201] for three years.[202]

In conclusion, the liver is the body's largest, most important organ, and is involved in a variety of physiological functions. Fatty liver is examined as alcoholic and non-alcoholic. Alcoholic liver steatosis is associated with increased consumption of alcohol, while it is not possible to show a single reason for non-alcoholic fatty liver disease. NAFLD is also referred to as MAFLD. The causes that may cause the disease can be many diseases such as obesity, sedentary life, hyperlipidemia, insulin resistance, T2DM. The prevalence of fatty liver is influenced by gender, age, sleep apnea, ethnicity, endocrine disorders. The course of the disease varies from cirrhosis to HCC. Causes of this disease are being investigated, more and more the efforts to treat it are increasing and the studies on the fatty liver are of interest. Many studies have been conducted on fatty and NAFLD. However, no single and definitive treatment is available. Different treatments are

preferred depending on many factors such as the characteristics of the patient, the degree of disease, and the cause of fatty liver. Nowadays, new methods are being researched and applied apart from the treatment methods from the past. Combining old and modern therapy strategies appears to be a viable option for treating ALD and NAFLD. In order to ensure trust and prove the effectiveness of these treatments, additional research should be undertaken on the treatments that will be acknowledged as the new therapy approach. In this way, the most appropriate treatment methods can be found and applied to patients.

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