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Non-Alcoholic Fatty Liver Disease "An Iceberg Phenomenon"– A Review of Diagnosis and Treatment Options.

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Abstract -

Non-alcoholic fatty liver disease (NAFLD) is the liver manifestation resulting from metabolic syndrome and is associated often with obesity, insulin resistance, dyslipidemia, and systemic hypertension. NAFLD includes a subset of disease that ranges from steatosis (NAFL) to non-alcoholic steatohepatitis (NASH). The condition gets complicated with the late manifestation of hepatic injury and chronic cirrhosis and even hepatocellular carcinoma. There are two theories that explain the pathogenesis of NASH namely the "second hit" theory and its modified version "multiple parallel hit" theory. Ultrasonography is the best examination to assess NAELD, however, the liver biopsy is the gold standard that is used to confirm the chronicity and late manifestations, particularly in determining NASH. Recently there are few significant non-invasive markers that are used in the diagnosis and prognosis of NAFLD. There is no proven treatment for NAFLD or NASH so far and treatment is mainly emphasizing bodyweight reduction and treating associated problems like insulin resistance, dyslipidemia, and hypertension. In this review, a clear overview is summarized of the best diagnosis and treatment options available for NAFLD and NASH using valid literature.

Keywords – (Non-alcoholic fatty liver disease, fatty liver, hepatomegaly, non-alcoholic steatohepatitis, dyslipidemia, liver cirrhosis, Hepatic cancer)

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of a wide range of liver diseases that includes a subset of disease that ranges from steatosis (NAFL) to non-alcoholic steatohepatitis (NASH). The condition gets complicated with the late manifestation of hepatic injury and chronic cirrhosis and even hepatocellular carcinoma. The clear definition for NAFLD is still controversial however when more than 5% of hepatocytes develop steatosis it can be identified as NAFLD when there is no associated viral hepatitis, alcohol overuse, or history of hereditary liver diseases [1]. Recently an international panel of medical experts came up with a concept of metabolic dysfunction-associated fatty liver disease (MAFLD) which clearly emphasizes the role played by cardiometabolic risk factors in clinical progression and treatment progression of liver disease. Notably, MAFLD was not accepted as an appropriate nomenclature by the American Association for the Study of Liver Diseases and the European Association for the Study of Liver Diseases which lead to its lack of familiarity in literature. [2,3]. Non-alcoholic fatty liver disease (NAFLD) is the liver manifestation resulting from metabolic syndrome and is associated often with obesity, insulin resistance, dyslipidemia, and systemic hypertension.

Epidemiology

NAFLD is the most common chronic liver disease that affects the creamy layer of society in particular simply because of the inflated rate of obesity and type II diabetes mellitus. Significantly, NAFLD is not only a disease in the developed country but also among the developing countries that are getting westernized, causing a significant burden on healthcare systems and professionals [2]. In countries like Australia, the prevalence of NAFLD is three times more than the sum of all the other liver diseases like hepatitis, alcoholic liver diseases, hereditary liver diseases, liver carcinoma, and so on. [4] The prevalence of NAFLD is more seen with advancing age with men being more affected than the female that can be attributed to food habits. Currently, there are more reports which claim that NAFLD is on a rise even among children and adolescents who are obese. The rate of progression to cirrhosis, development of hepatocellular carcinoma (HCC) among adolescents is higher compared to adults. [5,6]

Though NAFLD is rated as the most common liver disease, its prevalence varies widely in different countries ranging from 13·5% in Africa to 31·8% in the Middle East, which can be attributed to nutritional value and lifestyle. The genetic factor and poor socio-economic status also play a vital role in less prevalence of NAFLD in African countries compared to Europe and western countries. [8] it is estimated that less than 10% of NAFLD patients only develop cirrhotic complications or hepatocellular carcinoma, which happens over 10–20 years from the initial diagnosis, however, this number may vary based on the other factors pertaining to the individual's change in lifestyle, medication, and activity after being diagnosed. [9,10]

Clinical manifestation

The patients are classically present in the age group between 40-60 and give a history of diabetes mellitus (DM) or present with obesity [11]. There are no specific symptoms reported by the patients that give doubt about NAFLD to the physician, however, the presence of obesity or DM along with symptoms like general fatigue, dyspepsia, dull aching pain around the liver can be clinical findings that can drive a physician to go for further investigation to rule out NAFLD [12] Hepatosplenomegaly have also been reported among the NAFLD patients who have a body mass index of more than or equal to 40 kg/m (2). [13]

Potential Complications

NAFLD encompasses a wide range of disease continuum based on its progression and complications that range from steatosis that presents with or without mild inflammation termed the non-alcoholic fatty liver (NAFL) to necro-inflammatory subtype called non-alcoholic steatohepatitis (NASH). The main difference between them is the presence of hepatocellular injury and hepatocyte ballooning phenomena. The progression of NAFLD is driven by various factors among individuals and that makes the prognosis prediction clinically difficult. There is individual heterogeneity in the response to medication and other treatment interventions among NAFLD which contributes to dilemmas in clinical decision making and reasoning. Prognostic information can only be given to the patients using information about disease activity particularly the extent of liver fibrosis that has happened at the time of diagnosis. Metabolomics, genomics, primarily helps in the phenotyping of the disease and help in potential disease stratification, but these are still in a rudimentary stage of development yet a powerful future scope in management and prognosis prediction [14]. A proportion of patients with NAFLD develop NASH and the exact mechanism behind this pathophysiological progression is not yet clearly understood. However, there are two theories that explain the pathogenesis of NASH namely the "second hit" theory and its modified version "multiple parallel hit" theory [15,16]. The “single hit theory” explained that the liver gets hit by steatosis and cellular stresses like oxidative stress factors, apoptosis, and gut-derived lipopolysaccharide which results in the progression of NAFLD to NASH. [17] later studies that investigated the role of P*atatin-like phospholipase 3* (*PNPLA3*) gene polymorphism, revealed that it has a significant role to play in the progression of NAFLD to NASH. Now its clearly understood that even though NAFLD is a non-progressive disease, it gets the potential to become a progressive disease in patients having a risk allele of the *PNPLA3* gene. This concept is now widely and popularly called the “multiple hit” theory. [18]

Mortality rate

The progressive fibrosis that takes place in NASH renders it the most complicated form of NAFLD with a concomitant cardiovascular disease. Among the wide spectrum of NAFLD, NASH presents with the highest rate of mortality [19] Most strikingly it’s predicted that NAFLD which is the third reason for liver transplantation will soon top the table given its rate of occurrence and deterioration of lifestyle quality. [20] Necroinflammatory development like lobular inflammation and hepatocellular ballooning is associated with high rates of mortality among fatty liver disease. [21] Recently Pegah Golabi and colleagues found that the risk of mortality among people with lean BMI yet suffering from NAFLD was high because they presented with high visceral obesity, which was not sensitively measured by scales like BMI. These findings are so important in controlling the rate of progression and mortality in NAFLD which do not present with significant clinical features. [22] The higher mortality rate was observed with increasing age (with hazard ratio/decade, 2.2; 95% CI, 1.7-2.7), impaired fasting glucose (with hazard ratio, 2.6; 95% CI, 1.3-5.2), and hepatic cirrhosis (with hazard ratio, 3.1, 95% CI, 1.2-7.8). [23]

Risk factors

A recent study showed that non-insulin-dependent diabetes Mellitus (NIDDM) has been found to have the highest association with the risk of NAFLD patients developing fibrosis, cirrhosis-related adverse complications, and mortality. [24] patients with obesity that is marked by a body-mass index of more than 30 kg/m² presenting with dyslipidemia (i.e., low levels of high-density lipoprotein and high levels of triglycerides) were found to be a risk factor for both developing NAFLD and progression to adverse stages. Hypertension was also associated with an increased probability of severe liver disease. Overall, it was observed that the NIDDM contributed more as a risk factor than all other comorbidities put together. PNPLA3 gene variant and aging was also predominant risk factor for the development of NAFLD. [25,26]

Non-invasive methods of diagnosis for NAFLD

Non-invasive diagnosis of NAFLD is done routinely using two methods, firstly a biological approach that quantifies biomarkers in the serum sample of the patient and secondly physical approach which quantifies the liver dimension and structure using ultrasound or high-resolution imaging like magnetic resonance imaging (MRI) or magnetic resonance-based elastography techniques (MRET). High concentrations of aminotransferases (AMT) have been associated with NAFLD, which indicates a persistently elevated liver function. It is important to note that normal levels of AMT do not exclude the possibility of NAFLD.

Off late it is found that most patients present with a normal AMT concentration [27,28]. Whenever the AMT values are high, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values are also slightly above the normal value. During the initial stages of steatosis, AST/ALT ratio is normally less than one, however, this value reverses when there is progressive fibrosis. There is controversy about AMT values and their ability to

diagnose the degree of fibrosis or liver inflammation. [29] Gamma-glutamyl transferase (GGT) is a similar factor to AMT which is frequently elevated in NAFLD, and its increased value indicates a higher risk of fibrosis [30]. Alkaline phosphatase, serum ferritin, and transferrin saturation index have been reported to be altered in a good proportion of patients with NAFLD. Research is on in identifying the role of hepatic iron deposition and its prognostic value and its specificity to NAFLD [31]. An epiphenomenon seen in NAFLD is the elevated serum autoantibody level found frequently. Bilirubin and albumin levels are rarely affected, except in patients with cirrhosis. Incidentally, they also exhibit an increased prolonged prothrombin time, thrombocytopenia, and neutropenia. [32,33]

Grading and staging in NAFLD/NASH

Reliable and valid tools should be used in the clinical setup and in clinical trials to stage the NAFLD for which a valid scoring system is needed. steatosis, activity, fibrosis [SAF] score, and Fatty liver inhibition of progression [FLIP] algorithm was created to assess the stage of fatty liver in morbidly obese individuals. This scale was found to be sensitive and had a high inter rate reliability among pathologists and hence was recommended to be routinely used in pathology practice [34]. SAF score was closely related to ALT level and AST levels with a high statistical significance. In the same study, a comparison between transaminase levels in normal liver and pure steatosis was performed which did not reveal any statistically significant differences. This supports guides us not to include steatosis in the activity score, however, it has to be reported separately in evaluating the SAF score [35]. There are 3 recognized histological scoring systems that are currently in use: NAFLD activity score (NASH CRN-NAS) devised by the NASH clinical research network, followed by SAF, and the Brunt staging system [35-37]. The NAS is a numerical rating scale that develops an activity grade, that grades steatosis from 0 to 3, hepatocellular ballooning from 0 to 2, acinar inflammation from 0 to 3, and finally a separate fibrosis stage from 0 to 4. With a value of less than 3 (activity score), the NAS had a good correlation with an absence of histological diagnosis of NASH. Likewise, with a score of greater or equal to 5, the NAS showed a significant association with having a diagnosis of NASH [35].

Imaging techniques

Ultrasonography

Ultrasonography (USG) is the commonest choice and first-line imaging method for identifying hepatic steatosis. It is commonly available, accessible, well-tolerated, and cost-effective. The degree of steatosis can be qualitatively graded using USG as mild, moderate, and severe. Some studies recommended the use of an ordinal scale for grading the same. [38,39]. It is proved through a meta-analysis that USG was 85% as accurate and effective as liver biopsy in distinguishing the absence of steatosis from moderate to severe steatosis. [40] In conventional clinical practice, USG has a limitation in that it can only effectively report on steatosis with >2.5%–20% liver fat content, this results in miss interpretation of patients presenting with 5% of liver fat content, [41,42]. Likewise, the presence of high adiposity among morbidly obese is also a limitation of USG and things get even harder when there is a co-existing renal disease. [43,44] The European guidelines for the management of NAFLD in 2016, recommend USG distinctly as a first-choice imaging method among adults at risk of NAFLD. [45] USG reveals the features of NAFLD through the increased echogenicity, hepatomegaly, and importantly intra-hepatic vascular blurring. [46]

Magnetic resonance imaging

MRI is the most high resolution and definitive imaging tool available for qualitatively and quantitatively analyzing hepatic steatosis. The fat and water content contribute to the signal obtained from the liver on MRI. The differential count of protons in fat and water helps in locating the fat molecules through various MRI techniques. [47,48]. The sensitivity and specificity of MRI are very high in determining histologically confirmed steatosis, which is 76.7%-90.0% and 87.1%-91% respectively [49,50]. There are various techniques in MRI like the Frequency-selective method, chemical-shift-encoded method, and MR spectroscopy. These three techniques utilize the fat-water proportion differences to analyse fatty liver disease [51].

With fat saturation, the MRI images correlate with the water signal; without fat saturation, they display the sum of fat and water generated signals. Comparing these two signals hepatic fat can be quantified. In hepatic steatosis, when there is a more saturated fat accumulation, the images show relative attenuation of the signal compared to unsaturated fat images, whereas there will not be any difference between the two images in normal liver. Proton Density Fat Fraction (PDFF) is the most commonly used technique along with Magnetic resonance elastography and T1 waited imaging. Out of these, PDFF is highly validated and frequently employed as it provides a more reproducible evaluation of liver steatosis than a liver biopsy. [52]

Biopsy

Liver biopsy is made through a fine needle and is administered at an outpatient level in gastrointestinal clinics. It is the standard gold technique to receive liver tissue specimens from multiple depths in the hepatic parenchyma. The specimens are given to the pathologic anatomy department to get them screened under the electronic microscope and give positive results about chronic liver disease and NAFLD. It is a potentially harmless disease but should be done in accordance with ultrasonography and other imaging techniques. Physicians should take specimens from all the suspicious for fat infiltration liver lobes. There are a few risks of the liver biopsy technique like massive liver bleeding and patient pain at the injection spot. Almost 60% of the liver

biopsy risks occur two hours after the procedure, so hospitalization of the patient for at least one day is necessary. In rare cases, open surgery may require bleeding and reducing the risk of having bile and other liver secretions in the abdominal cavity. Liver biopsy will set the stage of the NASH/NAFLD disease but it's not the regular procedure for NAFLD patients as it will not change the therapeutic pathway. Microscopic findings of NAFLD may not differ from findings in other forms of alcoholic liver disease and inflammation like macrovesicular hepatic steatosis, hepatocellular ballooning containing the Mallory bodies, pericentral perisinusoidal fibrosis, lobular and portal inflammation, and Glycogen nuclei which is not a specific finding for NAFLD. [53-55] The appearance of normal, fatty, and cirrhosis liver are shown in figure 1.

Figure – 1 – Image of healthy, fatty, and cirrhosis liver.

Treatment of NAFLD –

Lifestyle Changes

The most significant treatment for NAFLD is to change the patient's lifestyle. The first intervention would be to reduce patients' weight and decrease their adjacent cardiovascular and metabolic risk factors. However, weight loss has shown that it's beneficial for the steatotic liver and certainly stops further liver fat infiltration. That could happen with calories deprivation and initiation of a daily exercise program. [56,57] Some studies have also shown that the adoption of a Mediterranean diet is also beneficial for the liver. Since that diet doesn't include many saturated fatty acids, hepatic lipogenesis and steatosis are radically decreased in patients following such a diet. Patients with NAFLD should have a realistic and easy-to-achieve diet or exercise program. They need to regulate their comorbidities like hypertension, diabetes, hyperlipidemia and reduce the fatty acids accumulated in their liver parenchyma. The lifestyle modification should be accompanied by the adopting efforts or strategies to avoid relapse and recurrent weight regain reversal of all the good efforts. [58]

Diet

Excess caloric intake results in obesity and causes enormous comorbidities that are leading risk factors for developing NAFLD. [59] it is proved that even only a modest 3–5 kg weight gain is associated with the development of NAFLD, irrespective of a normal or abnormal BMI. [60] Interestingly, it is observed that not only excess caloric intake but also the manner in which the food is consumed and how it is distributed throughout the day, can influence liver fat accumulation. The section of this review explains the phytochemicals and micronutrients that are essential for the management of NAFLD.

Curcumin - It's the active substance that is there in the turmeric fruit. Usually, curcumin is a natural spice and additive used in many Asian cuisines. Consuming curcumin could protect the liver by activating non-inflammatory agents like proteins SIRT1 and SOD1. However, curcumin consumption in larger proportions could lead to hemorrhagic episodes and aggravate gallstones and bile problems. [61]

Silymarin (milk thistle) - It's an extract from the plant silybin marianum. The active substance is a lot more hydrophobic, and for that reason, its bioavailability in the blood serum could become problematic. The use of silymarin in people with moderate to severe NAFLD has an anti-oxidant activity.

That helps to decrease the levels of transaminases which further leads to less invasive liver damage. In other words, the NAFLD will not easily progress to steatosis, fibrosis, and hepatocellular carcinomas. [62]

Vitamin E has some exceptional anti-inflammatory and antioxidative effects. Since NAFLD has been correlated with oxidation and inflammation within the liver cells, Vitamin's E role is explored in NAFLD treatment. Today Vitamin E is proposed for certain patients that have already progressed to NASH without any secure evidence that it can prevent liver fibrosis. It is necessary to monitor patients receiving Vitamin E for NAFLD and NASH since long-term therapy may be related to strokes and prostate cancer in male patients. [63,64]

There is enough medical evidence that L-ornithine and L-aspartate have an antioxidant and protective action on the liver cells. [65] Ornithine - It activates the urea enzymes within the liver cells. That makes liver cells produce more urea when they metabolize toxins, and other chemicals. [66] L-aspartate - It's converted to glutamate using the proteolytic action of the glutamine synthetase that is abundant within the liver cells. Glutamate has shown protective properties to liver cells. [67]

Pharmaceutical Treatment

No pharmaceutical agent has been specifically approved for the treatment of NAFLD. Here is a list of drugs currently used for the treatment of NAFLD and NASH:

Anti-Diabetic Drugs Used To Treat NAFLD

Metformin - It has not been approved for NAFLD, however, there are many clinical trials in several controlled groups that offer optimistic results. Metformin has been the drug used for the first stages of type 2 Diabetes Mellitus. It reduces the resistance to insulin and makes it easier to improve the glycemic index in such patients. Although Metformin could help with diabetes treatment it hasn't shown any histological impact on NAFLD patients. That means it cannot stop the disease's progress or even treat NAFLD in the long run and reverse the liver damage. [68]

Pioglitazone - It has received a license to treat type 2 diabetes mellitus targeting both inflammation and adipose tissue metabolism. It has been shown that Pioglitazone may reduce the fat infiltration of the liver by enforcing the adipocytes to uptake the fatty acids from the liver cells. Another beneficial action of Pioglitazone is that it increases adiponectin secretion, a protein with anti-steato-genetic abilities. [69] However, Pioglitazone's effectiveness has many side effects, including weight gain and an uncertain role of this molecule to control fibromatosis of the liver parenchyma.

GLP-1 Receptor Agonists – Liraglutide - The GLP-1 agonists are molecules resembling the endogenous GLP-1 but have a longer half-life and thus remain in the bloodstream for more time. They stimulate insulin secretion, block the glucagon secretion from the liver cells, and delay the gastric pass of nutrients from the stomach. [70]

LP-1 may also increase weight loss in healthy individuals by activating the thermogenesis to the brown adipose tissue. Trials have shown that patients with NASH are 30% more benefited from reducing their liver fatty cells when taking GLP-1 (liraglutide) than placebo. [71]

Dulaglutide - It's a GLP-1 agonist that has shown a critical effect on reducing the hepatic cells' resistance to insulin and the insulin-like growth factor. It has been readily available in ampules that are disposable and prefilled devices adjusted to diabetic patients' skin. Studies have shown that a single administration of 1.5mg weekly could severely impact insulin resistance in patients with Diabetes Mellitus and improve the pathophysiology of the liver. In other words, it can relent the progress of fibrosis steatosis and NASH disease to patients diagnosed with early NAFLD symptoms. Dulaglutide has also improved the liver enzyme profiles reducing their high levels and making it easier to deal with such patients. [72]

Semaglutide - Semaglutide is a rather new GLP-1 analog with a lot of success in the symptoms control of diabetes mellitus, especially in the early stages of the disease. However, it has shown very good results in patients with NAFLD who have managed to take it once a week when administered in the intramuscular form or once per day when administered in the oral form. Studies have shown that Semaglutide is the GLP-1 analog with the highest reduction rate of ALT hepatic enzyme levels. That piece of evidence may show progress to patients who have an increased level of danger suffering from steatosis and fibrosis or even malignancies due to the NAFLD. [73]

Dipeptidyl peptidase-4 inhibitors (DPP4i) - It's a whole new category of medications approved for diabetes mellitus treatment. These drugs address the higher levels of DPP4 in the blood serum of patients suffering from active liver disease. [74] Patients receiving sitagliptin for four consecutive months at least once per week have shown a significant reduction in the liver enzyme levels when there is an active NAFLD diagnosis. However, other studies have shown no statistically significant progress in NAFLD disease to patients who receive it on a regular basis. For that reason, sitagliptin is not a drug with NAFLD's current management importance. [75] Vildagliptin has been approved by the EMA to treat diabetes mellitus in patients who have been suffering from adjacent liver disease. It seems like in many studies with patients with active NAFLD, Vildagliptin has managed to regulate the levels of hepatic enzymes and at the same time, decrease the internal liver levels of triglycerides. All these patients have shown a significant improvement in the MRI and ultrasound of FibroScan imaging methods for steatosis and fibrosis of their liver, respectively. [76]

Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) - These are molecules called gliflozins and have a glucose-reducing effect on patients with diabetes mellitus and liver disease. They can improve metabolism levels and help obese patients with their efforts to lose weight. Here are the most promising gliflozins representatives reported in studies for potentially active NAFLD drugs.

Dapagliflozin **-** It is one of the first agents to get FDA approval in 2012 for diabetes mellitus. However, it has shown significant good results in reducing the liver enzyme levels, liver stiffness, and the infiltration of the liver with fat when an active NAFLD has been diagnosed. However, there is little or no evidence for the beneficial activity of Dapagliflozin in patients with active NASH disease. [77]

Canagliflozin **-** It has been the first SGLT2i approved for use in the United States, administered to patients with severe diabetes mellitus and active liver diseases. In clinical trials with NAFLD patients, Canagliflozin has shown a significant reduction in the hepatic enzymes and has improved liver biopsy in active NASH patients. More specifically, Canagliflozin has managed to reduce the signs of inflammation, cell ballooning, steatosis, and fibrosis. That's why it's the most promising drug agent to be approved for the treatment of NAFLD in the following years. [78]

Empagliflozin **-** It was approved in 2014 by the FDA to treat patients with diabetes mellitus with adjacent cardiovascular problems and comorbidities. Its primary action is to reduce the liver enzymes ALT and AST to patients with severe hepatic disease and inflammation. It has also relieved patients with severe NAFLD from further liver steatosis and fibrosis, as detected by MRI and other ultrasound imaging techniques. There is a large-scale trial ongoing to ensure its safety for all patient groups, and Empagliflozin would be the drug of choice for treating severe to moderate NAFLD. [79]

A-Glucosidase Inhibitors **-** They act as inhibitors for the a-glucosidase, that is the enzyme allowing sugar and starches to enter the epithelial cells in the small intestine. As a result, starches and sugars cannot get absorbed and that lowers the sugar blood levels to patients suffering from diabetes mellitus and other liver diseases. A combination of Ezetimibe and acarbose has shown a significant reduction in steatosis, fibrosis, and inflammation in mice who had NAFLD. Further research on humans about potential side effects should be done in the following years to establish drug therapy as the first-line treatment for NAFLD. [80,81]

Non-pharmacological management

There are many food supplements that give beneficial results in NAFLD. Though many food and bioactive Compounds are effective there needs to be extensive research to find the safe and effective doses for optimal results. There are some controversial results that are documented in different studies against the use of phytochemicals. Consumption of oranges more than seven times a week had been proved to have increased the risk for NAFLD which is due to the overload of fructose [82]. To prove the contradicting views in this regard there is one more study in Japan that established no relationship between fruit consumption and NAFLD and in fact insisted Japanese consume more fruits and stay healthy. [83]

Consumption of coffee also has a risk for NAFLD according to a few researchers however coffee is proven to reduce the risk of liver fibrosis and cirrhosis. [84]

The bioactive compounds found in food that are having anti-oxidant property can prevent steatosis by removing free radicals generated by the dead cells. There are many phytochemicals like Resveratrol (3,5,4-trihydroxy-trans-stilbene) which is abundantly present in grape, raspberries, peanuts, and red wine is an excellent antioxidant that can prevent metabolic diseases and thereby contribute to liver function. In addition, they control the optimal production of liver enzymes and lipid storage and help resolve NAFLD. [85]

Anthocyanins (flavonoids) – literature is concordant on the fact that Anthocyanins are a capable potential suppressant of hepatocellular lipid deposition by inhibiting lipogenesis and possibly promoting lipolysis. Furthermore, Anthocyanins also diminish cellular oxidative stress by facilitating the antioxidant response. [86-88]

The other bio element that is very effective in NAFLD is lycopene. A cohort study on 2,687 subjects illustrated that the higher serum values of lycopene was positively correlated with NAFLD prognosis in middle-aged and geriatric patients [89]. Likely, a community-based quantitative study involving 2,935 patients aged 40–75 years conveyed that lycopene was inversely correlated to NAFLD prevalence with an odds ratio of 0.54; 95%CI: 0.42, 0.68) [90].

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) - curcumin itself acts removing free radical and scavenger of dead cells. With its phenolic, β-diketone and methoxy group it acts as an effective antioxidant and helps rejuvenate of the liver cells. Further clarification is needed regarding the structure-activity relationships and molecular mechanisms of this phytochemical in oxidative-associated liver diseases. [91]

Conclusion

NAFLD has become an epidemic in western developed countries because of the increased life expectancy and the high prevalence of obesity in all parts of the general population. A simple liver ultrasound combined with some biochemical and immunological tests is enough to pose NAFLD's first diagnosis to otherwise healthy individuals. It's important to refer patients suspicious of NAFLD to the relevant hepatologists for elastography and CT scan to ensure that NAFLD has not progressed to NASH of cirrhosis. Patients with type 2 Diabetes Mellitus and cardiovascular diseases should be the first to be screened for NAFLD. A sincere change in their lifestyle, the abolishment of saturated fats from their diet, and the consumption of many more fruits and vegetables when adopting a healthy exercise program could reverse the NAFLD progress at any stage. Modern pharmaceutical agents are yet to be licensed by national health authorities and give hope that NAFLD will be easily treated in the near future. Alongside widely available new imaging techniques that are affordable for the median patient could eliminate the morbidity of NAFLD that has been a major concern and a prime cause for hepatocellular carcinoma in western countries. There is an enormous scope through nonpharmacological management of NAFLD with many phytochemicals like

Resveratrol, Anthocyanins, lycopene, Curcumin, Psyllium, and vitamin E. However more research is needed in this area to establish a clear idea of dosage, indication, and limitations.

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