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Non Alcoholic Fatty Liver Disease

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Annotation: Health care providers divide fatty liver disease into two types. If the fat accumulate but no damage to liver occur, the disease is called nonalcoholic fatty liver disease (NAFLD). If fat accumulate in liver plus signs of inflammation and liver cell damage, the disease is called nonalcoholic steatohepatitis (NASH). Non-alcoholic fatty liver disease (NAFLD) is a common disorder and refers to a group of defects where there is accumulation of excess fat in the liver of people who drink little or no alcohol. The most common form of NAFLD is a non-serious condition called fatty liver. In fatty liver, fat accumulates in the liver cells. Although having fat in the liver is not normal, by itself it probably does not damage the liver. A small group of people with NAFLD may have a more serious condition named non-alcoholic steatohepatitis (NASH). In NASH, fat accumulation is associated with liver cell inflammation and different degrees of scarring. NASH is a potentially serious condition that may lead to severe liver scarring and cirrhosis. Cirrhosis occurs when the liver sustains substantial damage, and the liver cells are gradually replaced by scar tissue which results in the inability of the liver to work properly. Some patients who develop cirrhosis may eventually require a liver transplant.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver metabolic dysfunction

disease and encompasses a broad spectrum of pathological processes ranging from steatosis to nonalcoholic steatohepatitis, and subsequent hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma , (NAFLD) is the most common liver disease in the Western world , The term "nonalcoholic steatohepatitis" (NASH) was introduced by Ludwig in 1980 following observations of patients, mainly obese women, with histological evidence of alcoholic hepatitis on liver biopsy without a history of alcohol abuse [1]. in 2016, a meta-analysis of studies published between 1990 and 2015 provided evidence that the global prevalence of NAFLD was about 25%, making it the most common cause of chronic liver disease (CLD) [2]. in the United States, one-third of the overall population has NAFLD and 2%-5% have NASH , within the NAFLD spectrum, only patients with histologically proven NASH develop progressive liver disease, Progression is more likely in the setting of diabetes, insulin resistance (IR) and other pre-existing conditions [3]. the subsequent data from the Global Burden of Disease (GBD) study have supplemented this data and provided evidence that NAFLD is the most rapidly increasing global contributor to the disease burden related to the complications of CLD, including cirrhosis and liver cancer , Furthermore, the most recent data from the United States' United Network of Organ Sharing (UNOS) indicates that currently NAFLD is the second indication for all liver transplants and is rapidly becoming the top indication for liver transplant among those who are listed for hepatocellular carcinoma, This rapid increase is driven by the pandemic of obesity and type-2 diabetes mellitus (T2DM), In this context, the number of metabolic conditions that one carries not only increases the risk of having NAFLD but also the risk of progression to advanced liver disease and mortality, Besides adverse clinical outcomes such as increased mortality [4]. in addition to obesity and T2DM, other environmental and genetic factors may predispose these patients to progressive liver disease, its pathogenesis involves a multiple-hit process, which is recognized as the disruption of lipid and glucose metabolism , increasing evidence has demonstrated that insulin resistance (especially hepatic insulin resistance) often observably affects lipid and glucose homeostasis ,in the liver, insulin facilitates fatty acid re-esterification into triglycerides as well as glucose uptake for glycogen storage or glucose oxidation ,interestingly, insulin sensitizers, such as pioglitazone and metformin, have been showed to be able to potently attenuate biochemical and histological changes of NAFLD in clinic , however, long-term usage can cause bone loss and weight gain and increase the risk of bladder cancer, congestive heart failure, and lactic acidosis ,thus, there is an urgent need to explore non-toxic, safe, and effective drugs to treat NAFLD [5] .

AIM OF STUDY

The aim of this study was to determine:

1- The causes of non-alcoholic fatty liver disease

2- Comparison of properties of NAFLD and NASH

3- Pathological NAFLD and their treatment

NATURAL HISTORY

NAFLD was largely unknown prior to 1980 but is now recognized as the most common chronic liver disease in the US and many other parts of the world. The prevalence of NAFLD, as determined by population studies using ultrasound and serum enzymes, is estimated at 23%–30% [6]. The prevalence is expected to increase as the incidence of obesity and type 2 diabetes mellitus increases. While such studies do not distinguish NASH, the progressive form of the disease, from bland steatosis, it has been suggested that the prevalence of NASH is 5.7%–17% of the general population [7]. NAFLD may lead to NASH, cirrhosis and in some cases, hepatocellular carcinoma ,Fifty percent of patients with NAFLD have NASH and 19% have cirrhosis at the time of diagnosis ,Once cirrhosis develops 30%–40% of patients will die of liver failure over a 10 year period , a rate that is at least equal to that seen with hepatitis C ,Hepatocellular carcinoma is an increasingly recognized outcome , Why some patients develop

progressive disease while most do not remains to be determined, although genetic factors may be involved [8] . Historically, liver injury is thought to be the result of the ”two-hit hypothesis” involving IR and altered adipokine production, resulting in oxidative stress and apoptosis [9] .The “two-hit hypothesis” was first described by Day et al , in 1998. The first hit represents accumulation of triglycerides (TG) and free fatty acids (FFA) from visceral adipose tissue in hepatocytes secondary to IR. FFA are transported to organs including the liver and undergo either β-oxidation in the mitochondria or are stored as TG.TG stored in the liver come principally from lipolysis of white adipose tissue, but also from dietary lipids and de novo lip genesis [10]. If an imbalance is present, excessive FFA flux and accumulation induce hepatic IR, Once hepatic steatosis is established, progression to steatohepatitis involves a “second hit”, consisting of inflammation, mitochondrial dysfunction, enhanced oxidative stress caused by reactive oxygen species, lipid oxidation and production of adipokines resulting in hepatocyte damage and fibrosis [11]. Fatty liver is susceptible to oxidative injury and lipid peroxidation,ien 2010 Tilg and Moschen, introduced the “multiparallel hit” hypothesis to explain NAFLD pathogenesis. This hypothesis stresses the importance of gut-derived and adipose tissue-derived factors that promote liver inflammation and fibrosis. This hypothesis, based on reports that endoplasmic reticulum stress, and cytokine-mediated stress can induce steatosis as well as necroinflammation, suggests that multiple “hits” act together in parallel in the development of NASH [12]. NASH clearly progresses to cirrhosis with further decompensation leading to death or liver transplantation in some individuals [13].

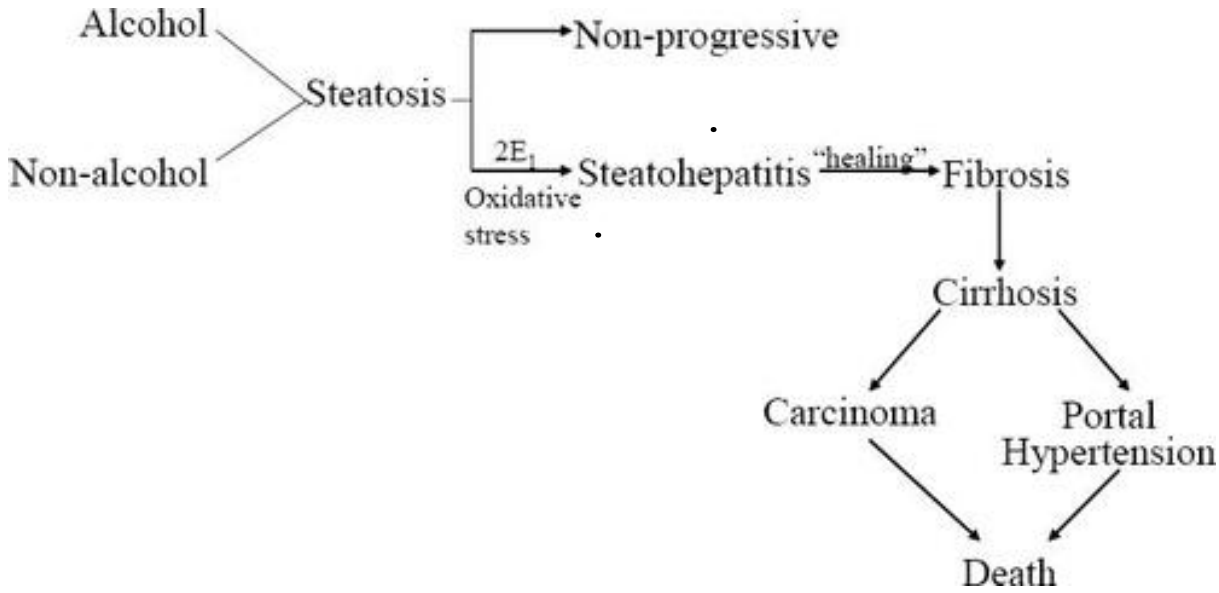

Fig.1 (The natural history of non-alcoholic fatty liver disease)

EPIDEMIOLOGY

There are remarkable epidemiological variations in relation to geografichal areas analysed, and in this case, the prevalence of the disease changes if we consider specific population groups, where , Most studies indicate that NAFLD is usually associated with metabolic syndrome, but studies in Asian countries also report NAFLD in non-obese individuals, however, these findings may be explained by the fact that, for a given body mass index (BMI), body fat content is usually higher in Asians than in westerners , In North America the prevalence of NAFLD in the general population is between 27% and 34%, whereas the prevalence of NASH is between 3% and 5% [14] [15] . However, if we consider the high risk population groups, in these areas NAFLD prevalence grows exponentially, precisely 75- 92% in obese subjects and 60-70% in diabetic ones [16]. This problem has a higher importance if we consider the diffusion of obesity and diabetes in the American population [17] .Indeed, one-third of the population consists of overweight subjects or obese people showing an increase of type 2 diabetes mellitus incidences doubled in the last decade , These data seem to be even more disconcerting in view of the fact

that this increase is mainly related to an increased diffusion of these pathological conditions in young and pediatric population, that have a higher life expectancy, Consequently, in the absence of an efficient therapeutic intervention, in the near future it will be possible to observe an increase in the prevalence of disease advanced stages and its hepatic and extrahepatic complications [18] .Indeed, both obesity and type 2 diabetes mellitus, are considered risk factors for the development of NASH and fibrosis [19] [20] . According to some references, people in advanced age and male gender have a higher risk of developing NAFLD, independently of presence or absence of metabolic syndrome [21] . in male gender, it is possible to observe an increase of the risk of NAFLD in the transition between young and median age until 50, NAFLD may be affected by genetic or environmental factors [22].

DIAGNOSIS

NAFLD encompasses a spectrum of diseases of different etiologies ranging from fat accumulation (steatosis) to inflammation and fibrosis (NASH) and finally cirrhosis, Formally, a diagnosis of NAFLD requires a liver biopsy with a lipid content of at least 5% of hepatocytes, In 20%-25% of cases, steatosis will evolve to NASH and, in turn, 20% of these patients will develop cirrhosis [23]. Liver biopsy is the current most standard for NASH diagnosis and staging, but the method is invasive and cannot be used in population-based studies. Only biopsy can assess inflammation and fibrosis, However, sampling variability may alter the accuracy of the diagnosis [24]. Several noninvasive diagnostic methods for NAFLD and NASH have been introduced recently, imaging techniques including proton magnetic resonance spectroscopy (1 H-MRS), ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) can be used, 1 H-MRS is considered the most accurate noninvasive method for measuring liver fat content. Ultrasonography is the most widely used method but is relatively insensitive, as it can detect steatosis only when liver fat content exceeds 33%, Other studies have used elevations in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as indicators of NAFLD, However, these measurements are neither sensitive nor specific, Indeed, up to 70% of subjects with NAFLD have normal levels of ALT and AST [25]. Different scoring methods have been developed for NAFLD screening, such as the Fatty Liver Index, and the Lipid Accumulation Product, These indices are easy to use, and could contribute to better assess NAFLD prevalence.

PATHOGENESIS

The liver plays a central role in lipid metabolism, importing serum free fatty acids and manufacturing, storing and exporting lipids and lipoproteins, However, the pathophysiology that leads to NAFLD is not well understood, in particular, the factors that lead to progressive hepatocellular damage after triglyceride accumulation are not well elucidated, it appears that alteration of local and systemic factors (particularly insulin resistance) that control the balance between the influx or synthesis of hepatic lipids and their export or oxidation leads to hepatic triglyceride accumulation ,the steatotic liver is then thought to be vulnerable to secondary insults, which lead to hepatocellular inflammation and fibrosis, a variety of factors have been implicated to produce a second “hit,” including hormones derived from adipose tissue (adipocytokines), oxidative stress and gut-derived bacterial endotoxin [26].

Insulin Resistance

The pathogenesis of insulin resistance is complex and is likely to involve many genetic polymorphisms that influence insulin secretion and action as well as environmental factors that promote obesity and immobility [27]. Hyperinsulinemia increases serum free fatty acid levels, which are taken up by the liver and drive triglyceride production and hepatic steatosis, in addition, chronic hyperinsulinemia promotes de novo hepatic lipogenesis through upregulation of lipogenic transcription factor ,and may activate profibrotic cytokines such as connective tissue growth factor [28] .

Hepatic lipid metabolism

Lipids are normally exported from the liver in very-lowdensity lipoproteins (VLDL), which are formed by microsomal triglyceride transfer protein (MTP) incorporating triglyceride into apolipoprotein B (apo B), A reduction in MTP activity and apo B synthesis and secretion may impair hepatic lipid export and favour hepatic triglyceride accumulation [29] .

Inflammatory and fibrotic mediators in NAFLD

Adipocytokines (tumour necrosis factor-α [TNF-α], leptin and adiponectin), free fatty acids, mitochondrial dysfunction, bacterial endotoxin and vascular disturbance have all been implicated in the development of hepatic inflammation and fibrosis in patients with NAFLD, these factors may be directly hepatotoxic or generate oxygen radicals with subsequent lipid peroxidation , cytokine induction and liver damage [30]. TNF-α promotes insulin resistance and liver inflammation , Levels are increased in patients with NAFLD, perhaps secondary to gut-derived endotoxin or TNF-α polymorphisms [31]. As a result of insulin resistance, serum free fatty acid levels are increased in NASH patients and may be directly hepatotoxic or produce damaging reactive oxygen species [32]. Oxidative stress may be exacerbated further by ultrastructural mitochondrial lesions, which impair respiratory chain function [33]. As liver injury progresses, fat-laden hepatocytes and perisinusoidal fibrosis may impair microvascular hepatic blood flow, this effect may decrease oxygen and nutrient exchange and thus stimulate a microvascular inflammatory response and an escalating cycle of liver damage and vascular insufficiency [34].

Metabolic injury and hepatocytes

There are several intra- as well as extrahepatic triggers for inflammation in NASH that relate to the metabolic injury to the liver, as they represent potential targets for pharmacological intervention, Insulin resistance is nearly always present in NAFLD, and there is a strong association between insulin resistance and the development of hepatic steatosis [35] .The visceral adipose tissue itself is not only involved in impaired insulin metabolism but also contributes to the generation of a systemic inflammatory environment through the secretion of inflammatory cytokines such as CC-chemokine ligand (CCL) 2 , alterations in the gut–liver axis represent another extrahepatic trigger for hepatic inflammation as NASH is often associated with intestinal dysbiosis , intestinal dysbiosis in combination with intestinal barrier dysfunction is thought to lead to increased bacterial translocation and higher secretion of inflammatory cytokines and interferons (IFNs) , which in turn activate intrahepatic inflammatory pathways. For instance, more circulating endotoxins can be detected in NASH, Recent work has even demonstrated the influence of the microbiome on the localization of immune cells within the liver [36]. Intrahepatically, metabolic injury primarily affects hepatocytes. In addition to inflammatory stimuli from the circulation, glucose and lipid metabolism within the hepatocytes become dysbalanced , in particular, nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) and farnesoid X receptor (FXR) play a crucial role in this process [37] . Accumulation of free fatty acids in hepatocytes increases the presence of lipotoxic intermediate metabolites such as palmitates, stearates, and ceramides , These lipotoxic metabolites as well as cholesterol and fructose can induce endoplasmic reticulum (ER) stress and mitochondrial dysfunction , ER stress causes an increased production of reactive oxygen species (ROS) , Mitochondrial dysfunction impairs the primary metabolism of free fatty acids by β-oxidation, which can then accumulate further and are alternatively oxidated in peroxisomes and cytochromes generating even more ROS [38] . In the course, there is an increase in oxidative stress, loss of ATP, and subsequent decrease in mitochondrial integrity, which ultimately leads to cell death of hepatocytes, Accumulation of cholesterol may additionally disrupt membrane fluidity ,and directly activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome , Collectively, these processes ultimately lead to apoptosis or necrosis of affected hepatocytes via membrane disruption and consequent release of proteases into the cytoplasm [39].

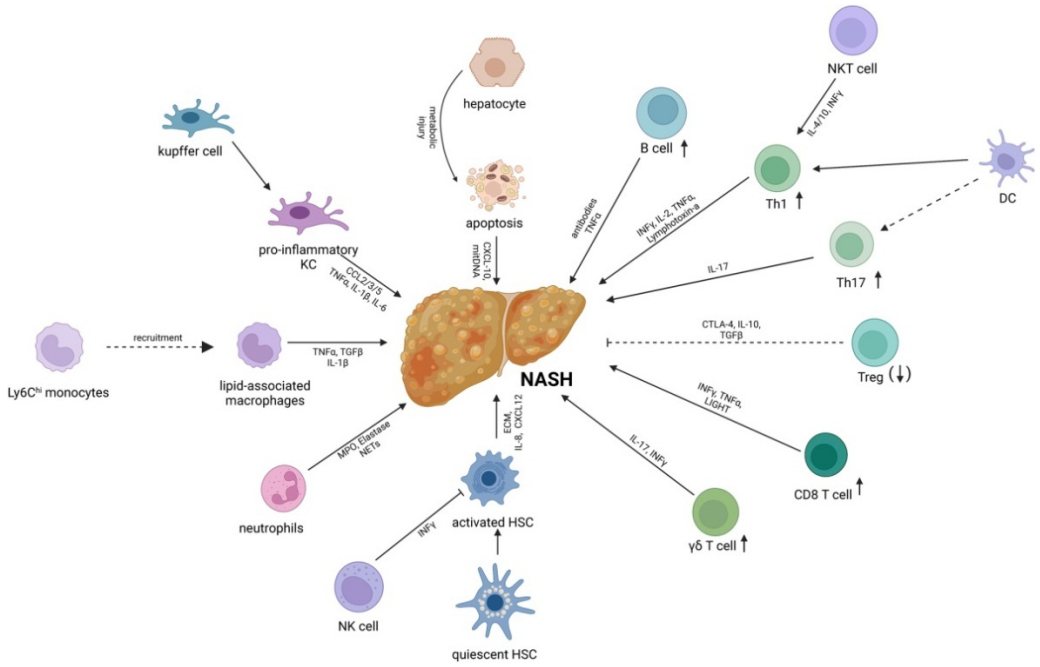

Figure 2: Overview of immune cells involved in the pathogenesis of NASH.

Intra- and extrahepatic triggers can lead to the activation of different immune cells in NASH, which includes various cell types of the innate and also the adaptive immune system. Kupffer cells, as the most frequent resident immune cells in the liver, adopt an inflammatory phenotype and activate other immune cells by releasing inflammatory cytokines. As inflammation progresses, Kupffer cells are replaced by monocyte-derived macrophages. Also, other immune cells as neutrophils and Type 1 T helper cells contribute to the inflammatory environment in NASH. However, also anti-inflammatory effects of immune cells in NASH are described for special subsets for natural killer cells and possibly for regulatory T cells. In addition, the effects of different cell types can differ between different stages of diseases. Thus, this figure can only provide a simplified overview of some of the relevant mechanisms. CCL, CC-chemokine ligand; CCR, CC chemokine receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCL, chemokine (C-X-C motif) ligand; DC, dendritic cell; ECM, extracellular matrix; HSC, hepatic stellate cells; IL, interleukin, IL; INF, interferon; KC, Kupffer cells; mitDNA, mitochondrial DNA; MPO, myeloperoxidase; NASH, non-alcoholic steatohepatitis; NET, neutrophil extracellular trap; NK, natural killer cells; NKT, natural killer T cells; TGF, transforming growth factor; Th cells, T helper cells; TNF, tumor necrosis factor; Tregs, regulatory T cells.

Neutrophils

neutrophils are activated by DAMPs, PAMPs, cytokines, and apoptotic bodies and are recruited to the injured liver , Thus, increased infiltration of neutrophils in the liver is observed in biopsies of NASH patients. CXCL1 and IL-8, among others, play an important role in their recruitment , Activated neutrophils produce proinflammatory mediators and secrete typical peptides from their granules, including neutrophil elastase, myeloperoxidase (MPO) and lipocalin-2, the amount of which is also increased in NASH [40] . MPO enhances hepatocyte injury and macrophage activation , However, in addition to these proinflammatory mechanisms, there is also some evidence of anti-inflammatory effects of neutrophils. For instance, microRNA (miR)-233, which is mainly found in neutrophils, is increasingly expressed in human NASH livers and probably represents a protective mechanism ,Via effects on lipid metabolism and macrophage polarization, miR-233 contributes to the inhibition of disease progression. Its deletion results in increased NASH in animal models [41] .

Natural killer cells

Natural killer (NK) cells participate in the inflammatory pathogenesis of NASH , After their

activation, they are able to produce IFNγ and thus induce an inflammatory polarization of macrophages , Although IFNγ also appears to have an antifibrotic effect, this effect has been shown to be diminished in patients with insulin resistance and NASH,Nonetheless, NK cells may also have antifibrotic activities by inducing de-activation and cell death of HSCs [42] .

Dendritic cells

Myeloid dendritic cells (DCs), also called classical DCs (cDCs), represent an important link between the innate and the adaptive immune system. While a protective effect against hepatic inflammation was initially postulated in mouse models , proinflammatory effects for different subsets of DC became apparent over time. In particular, a subset of $XCR1^+$ subset of cDC type 1 was described in mice and humans that seems to favor the development and progression of NASH [43] . A possible therapeutic approach to interfere with proinflammatory cDC represents the inhibition of fractalkine receptor CX3CR1, which is involved in the recruitment of cDC. Treatment with an antagonist showed reduced infiltration with cDC and improved hepatic inflammation in mice , Overall, however, the contribution of DCs in NASH is not yet fully understood [44] .

T and B lymphocytes

In addition to the described effects of the innate immune system, more and more influences of the adaptive immune system in NASH are being described ,Their interactions and influences are less well understood than those of the innate immune system, but it is well-known that infiltration of lymphocytes is a histological feature of NASH in patients , In this context, the degree of infiltration correlates with parenchymal damage and inflammation. Animal models with knockouts leading to an absence of mature B and T cells show less liver damage and inflammation ,This principally highlights the relevant role of lymphocytes in the pathogenesis of NASH [45] .The increased secretion of IFNγ in NASH causes T helper cells (T_h cells) to polarize more toward T_h1 cells in mice ,These T_h1 cells in turn produce additional proinflammatory cytokines, including IFNγ, IL-2, TNFα, and lymphotoxin-a, and modulate the stimulation of macrophages to an inflammatory phenotype,T_h17 cells have also been described to be more abundant in NASH, which has been linked to increased production of IL-17 although the specific mechanisms remained unclear [46] . The role of other T cells in the pathogenesis of NASH is insufficiently understood. While regulatory T cells (T_{regs}) are expected to have a more protective effect on NASH due to their inhibitory effects on $CD4^+$ and $CD8^+$ cells in the liver [47] . Another proinflammatory influence is attributed to B cells , especially the B2 subset. In patients with NASH, they form part of the inflammatory infiltrates and there is also an upregulation of B-cell activating factor (BAFF) ,In mouse models of NAFLD and NASH with B cell-specific deletions, a decrease of disease was shown, possibly mediated by reduced Th_1, which are otherwise activated by the proinflammatory stimulit of B cells [48] .

Interactions of immune cells with stellate cells

The various immune cells of the innate and acquired immune system present a large number of interactions with each other and with hepatocytes, which may contribute to the maintenance of inflammation and metabolic injury in NASH,However, to trigger progression from NASH to NASH-fibrosis, activation of the HSC, the main fibrogenic cell type in the liver, is required. Many of the triggers and stimuli already described are involved in this process. HSCs are considered the cell type with the highest number of interactions in the liver, including with immune cells in particular [49] .The variety of stimuli for HSC in NASH includes hepatocyte apoptosis, with apoptotic bodies and pre-apoptotic vesicles with inflammatory cytokines acting as DAMPs and being recognized by HSC). Activation of the NLRP3 inflammasome, may also occur directly in HSC [50] . Various inflammatory stimuli originate from immune cells, B cells activate HSC via TNFα and IL-8, $CD8^+$ via TNFα and IFNγ, NKT cells transmit activating signals via sonic hedgehog and osteopontin, and macrophages via transforming growth factor (TGF) β, platelet-derived growth factor, TNFα, ROS, and IL-1β , HSCs upon activation secrete

inflammatory cytokines and recruit additional immune cells , Most relevantly, activation of quiescent HSC leads to their differentiation and proliferation into inflammatory myofibroblasts which then produce high amounts of extracellular matrix, resulting in fibrosis [51].

Resolution of inflammation and fibrosis

Overall, the mechanisms involved in disease regression are less well understood, but immune cells play a relevant role in this process as well (Feg 3), As already briefly mentioned earlier liver macrophages have the potential to transform into Ly6C^{lo} restorative macrophages in mice ,These have the potential to support the resolution of inflammation through the secretion of regenerative growth factors and anti-inflammatory cytokines. Additionally, there is also evidence that these cells lead to regression of fibrosis through apoptosis of activated HSC and degradation of the extracellular matrix. Also, neutrophils may improve inflammation through the secretion of different mediators, e.g. annexin A1, phosphatidylserine, and lactadherin [52]. Regression of fibrosis requires inactivation or apoptosis of HSC to prevent the further accumulation of collagen. Their apoptosis can be induced via FAS-FASL by CD8^{+} memory cells ,In animal models of chronic liver disease also γδ-T cells were able to induce apoptosis of HSC [53] .

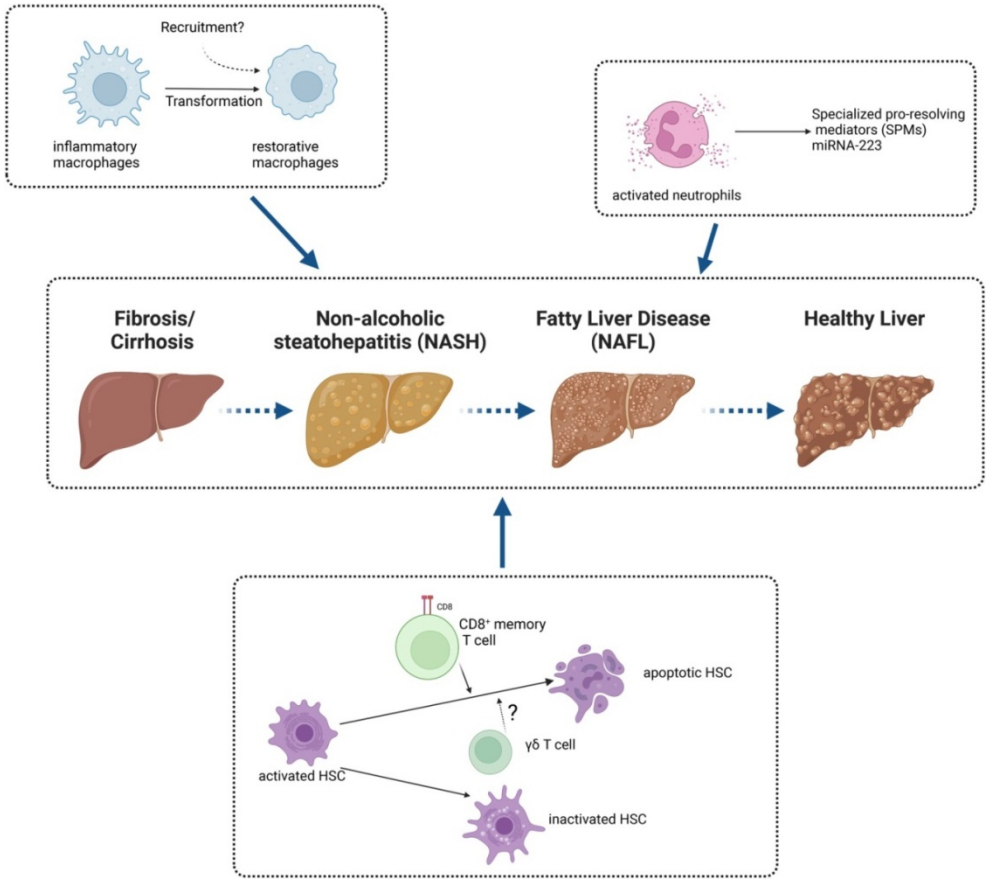

Figure 3: Overview of mechanisms of disease regression in non-alcoholic fatty liver disease

Regression of NASH involves apoptosis or inactivation of hepatic stellate cells, a change in the phenotype of macrophages and secretion of specialized pro-resolving mediators – mainly by neutrophils. The layout of these mechanisms does not portray chronological order, rather different processes probably occur simultaneously. γδ T cell, gamma delta T cell; HSC, hepatic stellate cell.

ENDOCRINE DISEASES ASSOCIATED WITH NAFLD

Type 2 diabetes

NAFLD is a major risk factor for the development of type 2 diabetes, most likely because of its strong association with hepatic insulin resistance [54] . This is notably due to the fact that some

lipid intermediates are more likely to cause hepatic insulin resistance. Indeed, while triglycerides are usually considered inert, other lipids such as diacylglycerols and ceramides have been clearly involved in ngland, secreting bile into the intestine, but can also be considered as an endocrine gland. Indeed, the liver produces some important hormones or hormone precursors, such as insulin-like growth factor 1 (IGF-1), angiotensinogen, thrombopoetin and hepcidin. More recently, numerous hepatokines have been described [55]. Among them, the liver produces Fibroblast Growth Factor 21 (FGF21), a hormone also produced by the white adipose tissue. FGF21 has recently emerged as a key regulator in the metabolism of glucose and lipids [56]. FGF21 levels are increased in NAFLD and correlate with hepatic triglyceride content, thus FGF21 is considered an emergent biomarker of NAFLD [57]. In diet-induced obese mice, which already display increased levels of FGF21, suggesting a state of FGF21 resistance, chronic administration of FGF21 not only reverses hepatic steatosis, but also improves insulin sensitivity by notably decreasing hepatic diacylglycerol hepatic content and subsequent PKCε activation [58]. Altogether, these data suggest that the accumulation of ectopic fat in the liver, leading to NAFLD, plays an important pathophysiological role in the development of insulin resistance and type 2 diabetes, Modulation of hepatokines released by the liver, such as FGF21, could represent a therapeutic role in the treatment of NAFLD and NASH [59]. NAFLD is more prevalent in patients with pre-existing metabolic conditions than in the general population, Specifically, type 2 diabetes and NAFLD have a particularly close relationship, A cross-sectional study of patients under 65 with type 2 diabetes found a 69% prevalence of ultrasonographic NAFLD [60] .Among these, 87% were diagnosed with NAFLD after a liver biopsy [61]. Therefore, the prevalence of NAFLD is higher in patients with type 2 diabetes than in the general population.

Obesity

Here the prevalence of NAFLD ranges from 57% in overweight individuals attending outpatient clinics to 98% in nondiabetic obese patients [62] .The median prevalence of NASH in the obese population is 33%, ranging from 10% to 56%, Bariatric surgery is becoming a frequent treatment option and intra-operative liver biopsies are now frequently performed. For example, in a study by Boza [63] .the prevalence of NAFLD and cirrhosis in a cohort of obese patients undergoing gastric bypass surgery was 63% and 2%, respectively, In some studies, hepatic fat content cancelled the correlation of visceral fat with IR [64]. but in other studies there was an independent contribution of both visceral fat and IR to hepatic fat content, Interestingly, perivascular and epicardial lipid deposits are correlated with atherosclerosis and metabolic syndrome,Moreover, epicardial lipids are correlated with visceral fat, coronary artery disease, presence of NAFLD, and even the severity of liver fibrosis [65]. Due to age-related changes in body fat distribution, especially an increase in visceral fat, the prevalence of NAFLD increases with age [66].

Adipokines

Adipokines are cytokines secreted by adipose tissue that are involved in adipose homeostasis and lipid metabolism, Many adipokines are being studied as potential targets for new drugs [67].

Adiponectin

Adiponectin, an anti-inflammatory cytokine, is produced predominantly by adipocytes at a level inversely correlated with visceral fat content. Low adiponectin levels are associated with IR and type 2 diabetes, dyslipidemia, hypertension, and NAFLD [68]. Indeed, disruption of adiponectin receptors increases tissue triglyceride content, inflammation, oxidative stress and IR, Adiponectin can prevent lipid accumulation in patients with NASH by increasing β-oxidation and by decreasing synthesis of FFA in hepatocytes [69]. In human studies, high plasma levels of adiponectin are correlated with a decreased risk of developing type 2 diabetes , and lower adiponectin levels have been shown to be an independent risk factor for NAFLD, Adiponectin levels are correlated with NAFLD progression and are therefore a prognostic factor [70].

Vitamin D deficiency

The pleiotropic effects of vitamin D, particularly on metabolism and the immune system, are being increasingly studied, NAFLD has been associated with low 25-OH vitamin D levels. Notably, a recent meta-analysis found that NAFLD patients are 26% more likely to be deficient in vitamin D compared with controls [71]. However, in the study of Dasarathy, the control group was smaller in number, had a lower BMI and was not age-matched, These differences may influence vitamin D levels, as obese patients have lower vitamin D levels, It is unclear how vitamin D could prevent or slow the development of NAFLD, However, vitamin D has been shown to inhibit the proliferation of HSC, which express the vitamin D receptor [72]. and therefore could reduce the fibrotic process.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is an endocrine syndrome frequently encountered in young women of childbearing age, with a prevalence of 8–15% , PCOS is best defined by the Rotterdam criteria, that is, oligo/anovulation, clinical and/or biological signs of hyperandrogenism, and polycystic ovaries (by ultrasound) [73]. Genome-wide association studies have shown a relationship between PCOS and several genes involved in type 2 diabetes, such as THADA, INSR and HMGA2, and insulin resistance occurs in about half of women with PCOS [74]. A meta-analysis of 17 studies revealed that there is a significantly higher risk of NAFLD in women with PCOS than in a control group, Moreover, this association was independent of obesity and geographic region, but might be correlated with hyperandrogenism [75]. the prevalence of NAFLD in women with PCOS varies between 35 and 70%, depending on the diagnostic method used [76]. Regarding the association between PCOS and the histological severity of NAFLD, a study reported that among 200 women with PCOS, 6 of them had biopsy-proven fibrosing NASH, Compared with the 194 of 200 PCOS women who did not undergo biopsy, women with biopsy-documented NASH had lower HDL-cholesterol, higher triglycerides, higher fasting insulin, higher aspartate aminotransferase, and higher alanine aminotransferase [77]. Conversely, the prevalence of PCOS in women with NAFLD has been shown to reach 71% in one cohort , However, it is not clear whether PCOS is an independent risk factor for NAFLD, Overall, women with PCOS show a high prevalence of NAFLD, even independently of obesity and dysglycemia , Hyperandrogenism and insulin resistance play a key role in the pathophysiology of PCOS-associated NAFLD, although the exact mechanisms remain elusive, Further studies are needed to better understand the complex endocrine regulations in the interconnections linking PCOS with NAFLD, in order to notably establish whether treatment with anti-androgenic drugs may reduce the risk of NAFLD in women with PCOS [78].

Male hypogonadism

Male hypogonadism is a clinical syndrome defined by reduced testosterone secretion and/or spermatogenesis. Male hypogonadism can be caused by diseases of the testes (primary hypogonadism) or dysfunction of the hypothalamic–pituitary axis (secondary hypogonadism) , Studies in males have reported an association between low testosterone and increased visceral adipose tissue, insulin resistance, and dyslipidemia , Accordingly, higher levels of testosterone are associated with reduced visceral abdominal adipose tissue [79]. The association between low testosterone levels and NAFLD has been observed in several epidemiological studies, and a meta-analysis including 16 studies has confirmed this association between lower testosterone levels and NAFLD in men , Preclinical studies have shown that low levels or the absence of testosterone may cause hepatic steatosis through increased de novo lipogenesis ,Therefore, low testosterone may favor uncontrolled hepatic lipid accumulation, thereby leading to the development of NAFLD[80].

Osteoporosis

Evidence for an important triumvirate (NAFLD, osteoporosis and metabolic syndrome) is rising,

A complex crosstalk of mediators coming from the liver (fetuin-A), adipose tissue (leptin, TNF-α, adiponectin) and bone (osteopontin, osteocalcin, osteoprotegerin) may contribute to the development of NAFLD and metabolic syndrome, and the protective effect of obesity on bone mass is progressively challenged [81]. For example, insulin can increase bone formation by binding to the insulin receptor on osteoblasts, and leptin and adiponectin can suppress bone formation or stimulate resorption. Conversely, the bone also affects glucose metabolism, by secreting cytokines, hormones and peptides like osteocalcin which increase pancreatic β-cell function, Treatment of NAFLD may also have an impact on bone. Thiazolidinediones, which are peroxisome proliferator-activated receptor γ (PPARγ) agonists, improve insulin sensitivity and reduce hepatic fibrosis progression, but also increase bone loss and fractures, especially vertebral fractures in males with type 2 diabetes, Further studies are needed to better understand the interactions between osteoporosis and NAFLD[82].

Thyroid gland: Hypothyroidism

Hypothyroidism is a frequent endocrine disorder defined by thyroid hormone insufficiency [83]. Primary overt hypothyroidism is defined by an elevated level of thyroid-stimulating hormone (TSH) in association with low serum free thyroxine (T4) levels, while subclinical hypothyroidism is characterized by elevated TSH levels in association with normal levels of T4, Thyroid hormones are involved in various metabolic processes, including body fat distribution, lipid utilization, energy expenditure, and glucose homeostasis, Altered thyroid hormone levels may, therefore, participate in the development of NAFLD [84]. Indeed, individuals with hypothyroidism are more at risk of developing components of the metabolic syndrome such as impaired fasting glucose levels, obesity, and hyperlipidemia that are clearly associated with the occurrence of NAFLD, thus suggesting a close link between hypothyroidism and NAFLD [85].

Pituitary gland: Growth hormone insufficiency

Growth hormone insufficiency, GH and insulin-like growth factor-1 (IGF-1) insufficiency have recently been associated with NAFLD, progression to NASH and even liver cirrhosis. NAFLD is more common in hypopituitary patients than control subjects and patients with growth hormone deficiency (GHD) are likely to have an increased risk of developing NAFLD. In a Korean cohort of men with hypopituitarism, the frequency of NAFLD (diagnosed by abdominal ultrasonography) was significantly higher in hypopituitary men than in control subjects (32.5% *vs* 70.6%, $P = 0.001$),Severe GHD in hypopituitarism was associated with more advanced NAFLD, In one series NAFLD developed after 6.4 ± 7.5 years (median 3 years) in GHD patients [86]. In obese patients with NAFLD, the combination of FFA and oxidative stress products results in endothelial dysfunction and can be a coronary risk factor,Oxidative stress is an important feature of the pathogenesis of NAFLD,As IGF-1 is known to have antioxidative effects and improve mitochondrial function, low IGF-1 levels may enhance oxidative stress and promote NAFLD [87].

TREATMENT

Lifestyle modification with a focus on healthy eating, weight loss when needed, and regular exercise remain the cornerstone of therapy in adults [88]. and children ,When recommending healthy food choices, a Mediterranean diet has been shown to be a good alternative to a western diet [89]. Bariatric surgery can be a good option in selected patients and a long term follow up study has been shown to reverse NASH and even substantial fibrosis in some [90]. However, surgery is possible in only a minority of patients and there is clearly a need for pharmacological therapy ,Prior clinical trial data suggest that pioglitazone or vitamin E may be beneficial in non-diabetic NASH patients [91]. and the benefit of pioglitazone on reversing NASH and improving fibrosis was recently confirmed in diabetic patients, It probably makes sense that no single therapy will reverse NASH in all patients since different patients likely manifest the phenotype of NASH in response to different genetic predispositions and environmental exposure, In addition, a major challenge for taking potential treatments through to approval by government

agencies has been identifying meaningful trial endpoints. The field has moved forward due to the combined efforts to address these issues by regulatory agencies, industry, and academics [92].The peroxisomal proliferator activated receptor (PPAR) family of nuclear receptors sense the presence of lipophilic molecules and regulate gene expression accordingly. PPARα upregulates oxidative metabolism in the liver and PPARδ does so predominately in muscle it needs to be emphasized that once a diagnosis of NAFLD is established patients have increased overall mortality compared to non-NAFLD patients However, this increased mortality mostly comes from cardiovascular- rather than from liver-related outcomes, furthermore, cancer-related mortality is among the leading causes of mortality in NAFLD patients, mainly driven by extrahepatic malignancies followed by hepatocellular carcinoma [83]. Most importantly, once a diagnosis of NASH and/or advanced fibrosis (i.e. fibrosis stage 3 or cirrhosis) and/or portal hypertension is confirmed patients are at an increased risk for liver-related complications (i.e. hepatic decompensation and hepatocellular carcinoma) and liver-related mortality , Therefore, lifestyle modifications and treatment of underlying metabolic conditions should be performed in all NAFLD patients, while specific pharmacological treatment should mainly be aimed at patients with biopsy-proven NASH and fibrosis [93] .

Lifestyle factors

Diet, weight loss and physical activity are the cornerstone of every treatment for NAFLD and are recommended by both the American and European associations for the study of the liver [94]. Reducing calorie intake by at least 500–1000 kcal has been shown to reduce hepatic steatosis and insulin resistance, Energy restriction and exclusion of NAFLD-promoting components (i.e. processed food, products high in added fructose) are recommended by the EASL-NAFLD guidelines ,and generally speaking a “Mediterranean diet” should be recommended to all NAFLD patients [95]. Dieting ultimately leads to weight loss and weight loss per se has been a major link to achieving improvements in liver histology and even resolution of NASH or fibrosis. In a 12-month lifestyle intervention program in patients with type 2 diabetes, hepatic steatosis and incident NAFLD was significantly reduced [96]. most importantly, a study including 261 NAFLD patients with paired liver biopsies before and after lifestyle changes aiming at inducing weight loss found that a greater extent of weight loss is associated with improvement in histologic features of NASH with the highest rates of NAS reduction (100%), NASH resolution (90%) and fibrosis regression (45%) occurring in those patients with at least ≥10% of weight lost [97]. Nevertheless, it needs to be noted that only 30% of all subjects have lost at least ≥5% of their weight at week 52 (end of the study)—and this very much represents the real-life issue of a few patients achieving weight-loss targets. Finally, a large systemic review and meta-analysis have shown that weight loss (≥7%) generally is safe and improves liver histology and cardiometabolic profile in NAFLD patients [98]. Regarding physical activity, current guidelines recommend 150–200 min/week of moderate-intensity aerobic physical activities in three to five sessions ,Importantly, it needs to be emphasized that also in patients with advanced chronic liver disease (i.e. cirrhosis) mild-to-moderate exercise is safe, reduces the degree of portal hypertension and was not associated with an increased risk for variceal bleeding or other hepatic decompensation [99]. Most recently, a study investigating an intervention consisting of a hypocaloric diet and 60 min/week supervised physical activity in compensated cirrhosis with portal hypertension and a BMI >26 showed a significant decrease in the degree of portal hypertension after 16 weeks of intervention ,with a weight-loss of >10% being associated with an even greater decrease in portal pressure. Of note, no episode of clinical decompensation occurred during the intervention [100]. To summarize the cornerstone of every treatment in all patients with NAFLD should contain the following three components:

1. Mediterranean diet aiming to reduce the average daily calorie intake by at least 500–1000 kcal.
2. Weight loss induced by diet and physical activity aiming at losing at least 3–5% of body weight.

3. Moderate physical activity aiming at 150–200 min/week—also in patients with NAFLD-associated advanced chronic liver disease.

Pharmacological treatment options

Guideline-recommended pharmacological treatment options for NAFLD patients are scarce and currently, only Vitamin E and the proliferator-activated receptor gamma (PPAR-y) ligand Pioglitazone are recommended for selected patients by the European- and American Association for the Study of the Liver [101].

Vitamin E

The anti-oxidative effect of Vitamin E is thought to contribute to its promising results in randomized trials showing a significant improvement in NASH. In 2010, the so far largest randomized trial on Vitamin E was published , It included 247 adults with biopsy-proven NASH but without diabetes and compared Vitamin E (800 IU once daily) versus Pioglitazone (30 mg once daily) versus Placebo with the primary study endpoint defined as an improvement in histologic findings (improvement by 1 or more points in a hepatocellular ballooning score; no increase in fibrosis score; and either decrease of NAS to ≤3 points or of at least ≤2 points, with at least a 1-point decrease in either lobular inflammation or steatosis) ,Vitamin E treatment resulted in a significantly higher rate of NASH improvement (43% vs. 19%, $p = 0.001$) as compared with placebo, However, the grade of fibrosis did not improve , Most importantly, adverse events in the Vitamin E group were not significantly different compared to Pioglitazone or placebo [102]. A study evaluating the effect of Vitamin E on clinical outcomes in 236 NASH patients with bridging fibrosis or cirrhosis found that indeed 800 IE/day decreased the risk of death or transplantation and hepatic decompensation ,both in diabetic and in non-diabetic patients [103]. While the PIVENS trials only included non-diabetic NASH patients, it has been shown that Vitamin E treatment alone (800 IE/day) was ineffective in reaching the primary endpoint (two-point reduction in NAS from two different parameters, without worsening of fibrosis) in a randomized trial including 105 patients with type 2 diabetes and biopsy-proven NASH ,Again no improvement in fibrosis was seen [104]. Possible side effects of Vitamin E include an increased bleeding risk, prostate cancer, heart failure and hemorrhagic stroke and those should be discussed with the patient, even though they are rarely seen, Vitamin E is currently not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis and cryptogenic cirrhosis [105].

CAUSES

For many years, the “two-hit hypothesis” was the most widespread model of NAFLD pathogenesis. The “first hit” is defined as lipid accumulation in the hepatocytes. This hit increases the vulnerability of the liver to many factors that constitute the “second hit” and promote hepatic injury, inflammation, and fibrosis [106]. However, the traditional “two-hit” hypothesis of NAFLD pathogenesis has been replaced by the “multiple-hit” hypothesis in order to explain the several molecular and metabolic changes of NAFLD , The “multiple hit” hypothesis has provided a more accurate explanation of NAFLD pathogenesis as it includes multiple interlocking processes rather than just two hits. IR, lipotoxicity , innate immune activation, and microbiome on a background of genetics (PNPLA3) as well as diet (saturated fat and fructose) and sedentary lifestyle are the multiple factors that lead to NAFLD progression [107]. The metabolic syndrome is a constellation of cardiometabolic risk factors including increased visceral adiposity and an increase in IR causing impaired glucose tolerance and T2DM, dyslipidemia, and hypertension [108]. Previous studies have demonstrated that abnormal serum concentrations of sex hormones, thyroid hormones, and growth hormone can trigger the development of metabolic syndrome [109]. NAFLD, as a hepatic manifestation of metabolic syndrome, can be associated with a number of endocrine diseases including polycystic ovary syndrome (PCOS), hypogonadism, primary hypothyroidism, and growth hormone deficiency [110]. Despite being closely linked with obesity, NAFLD can also manifest itself in non-obese

individuals. In fact, about 10–20% of non-obese Americans may present with NAFLD , “Lean” NAFLD is most commonly seen in Asian individuals in whom the majority of “lean” NAFLD studies have been carried out, Between 7 and 18% of the non-obese population in Asia (including China, Korea, and Japan) may have NAFLD , In Japan, one study of 3271 individuals reported that 68.5% of obese patients and 15.2% of non-obese patients developed NAFLD , While “lean” NAFLD is still not fully understood, a number of metabolic factors have been linked with this diagnosis, For example, despite exhibiting a “healthy” body weight, “lean” NAFLD patients exhibited the same pattern of IR and free fatty acid (FFA) distribution as obese individuals [111]. Interestingly, many of these individuals exhibit a lipodystrophic phenotype in which subcutaneous lipid storage is impaired and hepatic lipid storage increases, which coincides with an increase in IR , Several genes have been shown to be involved in this type of errant metabolic profile including *PPARγ, c-fos, p85α*, *Phosphate Cytidylyltransferase 1 Alpha*, and *WRN* , The metabolic development of “lean” NAFLD can be most concisely explained by the idea that increased lipolysis overwhelms the body's ability to store lipids subcutaneously and this leads to free fatty acid accumulation in visceral areas of the body, including in the liver, This errant lipid metabolism drives IR and inflammation leading to NAFLD progression and is similar to NAFLD progression in more classic obesity-driven and T2DM-driven pathogenesis [112]. In both lean and obese individuals, one common theme of NAFLD metabolism is the prevalence of IR. In fact, among patients with T2DM, which is comorbid with IR, about 60% also exhibit NAFLD , IR is a hallmark of T2DM and studies have shown how T2DM increases the risk of developing NAFLD , Since obesity, T2DM, IR, and NAFLD are interlinked and display similar physiological developments (Fig.4) it has been difficult to ascertain which disorder comes first or which causes another [113]. In support of the bi-directional relationship between T2DM and NAFLD, the odds of developing T2DM are two times higher in patients with NAFLD than in those without NAFLD , The mechanism by which IR influences NAFLD is still being studied, but several key connections have been established,For example, adipocytokines can improve insulin sensitivity through adiponectin secretion; NAFLD seems to alter this pathway and decrease the production of adiponectin, thus enhancing IR [114].

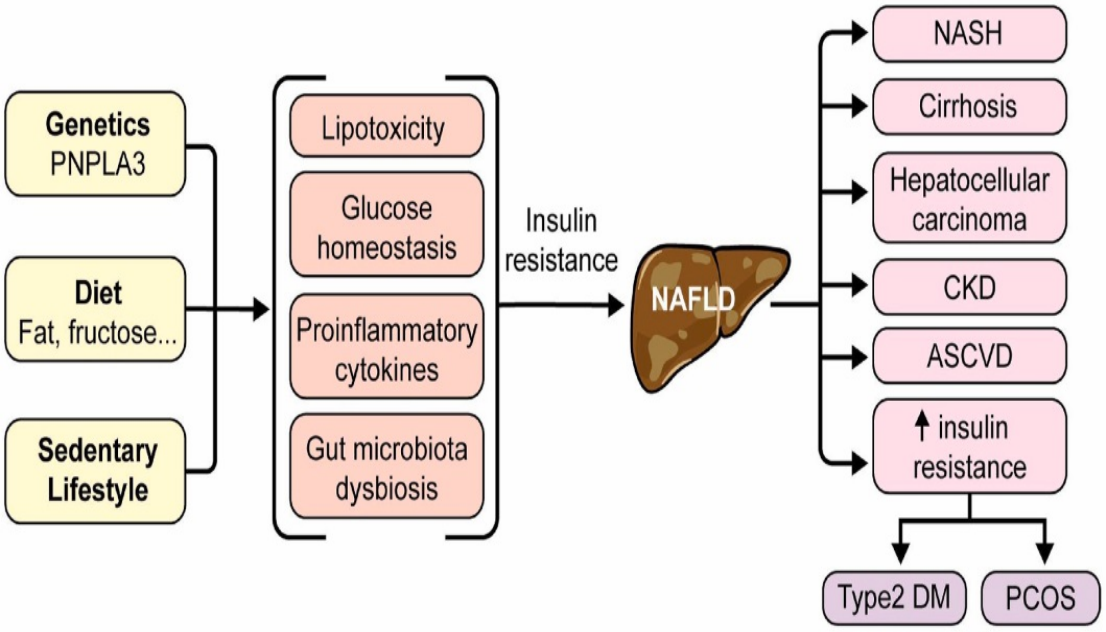

Fig.4: NAFLD (non-alcoholic fatty liver disease) stems from a combination of genetics, diet, and lifestyle, which drives dysbiosis and other metabolic malfunction.

The result is insulin resistance (IR) that drives NAFLD progression. As NAFLD progresses to NASH (non-alcoholic steatohepatitis) and HCC (hepatocellular carcinoma), IR progresses as well and contributes to the development of ASCVD (atherosclerotic cardiovascular disease), PCOS (polycystic ovary syndrome), T2DM (type 2 diabetes-mellitus), and CKD (chronic kidney

disease).

The mechanism by which NAFLD alters adiponectin production is still being studied, but research has established that adiponectin concentrations are influenced by genetics, diet, nutrition, exercise, and abdominal adipose tissue, all of which have been implicated in NAFLD pathogenesis, Adiponectin decreases IR through several methods, it inhibits the production of inflammatory cytokines that contribute to IR such as tumor necrosis factor-alpha (TNF-α) and interleukin-18 (IL-18) [115]. IL-18 is a known mediator of hepatic cellular injury and its inhibition can prevent the destruction and dysfunction of hepatic cells, Adiponectin also possesses anti-fibrotic activity by inhibiting the synthesis of key proteins and genes involved in fibrotic tissue development. In fact, adiponectin levels have been shown to be a diagnostic indication of NAFLD and upregulating adiponectin experimentally could represent a future treatment for NAFLD, although more studies are needed to corroborate such an assertion, Obesity is a significant independent risk factor for NAFLD development and progression, A study of 381,655 individuals reported that obesity increased the odds of NAFLD 3.5 fold [116]. This robust meta-analysis was controlled for confounding conditions including diabetes, hypertension, alcohol intake, and physical activity. In addition, each unit increase in BMI was positively correlated in a dose-dependent fashion to NAFLD risk , Similar to claims by other authors, Liet al's reasoning for obesity-mediated NAFLD risk is based on increased IR and inflammation [117]. Obesity stimulates inflammation via TNF-α, which enhances IR , Abnormal mitochondrial activity in the liver has also been shown to increase inflammation and, subsequently, enhance IR , The mechanism by which increased adipose tissue in the liver produces increased inflammation and IR involves the proliferation of M1 macrophages that secrete pro-inflammatory biomarkers including IL-6 and TNF-α ,These biomarkers activate downstream signaling cascades, which have been linked with IR [118]. Visceral adiposity plays an important role in the pathogenesis of NAFLD, Adipose tissue secretes pro-inflammatory cytokines including TNF-α and IL-6, Previous studies showed that the severity of steatohepatitis and fibrosis correlates with a higher level of TNF-α, Il-6 and TNF-α contribute to IR by interfering with the activation of the insulin receptor substrates, IR causes increased lipolysis of visceral fat by reducing the glucose uptake into the muscle [119]. Excess dietary carbohydrates and fatty acids from adipose tissue or de novo lipogenesis in the setting of IR play an important role in the pathogenesis of NASH [120]. Excess carbohydrates are converted to fatty acids through the multi-enzyme process , Excessive accumulation of fatty acids may lead to the production of lipotoxic agents which cause endoplasmic reticulum stress, mitochondrial dysfunction, hepatocellular injury, inflammation, and apoptosis, Hepatocellular response to lipotoxic stress is regulated by the gut microbiome, cholesterol, uric acid, and possibly periodic hypoxia [121]. Oxidative stress has been suggested as the main triggering factor for the progression of steatosis to steatohepatitis and also as a prominent feature of NASH [122]. Bergichio and et alproposed that genetic and environmental factors are potential contributors to hepatic steatosis and inflammation via the production of reactive oxygen and nitrogen species (ROS/RNS) [123]. The spleen is an important organ in the regulation of immune function and physiological inflammation. It is, therefore, worth identifying the effect, if any, that NAFLD can have on splenic function, Several studies have shown how patients with NASH exhibit increased splenic volumes and higher levels of several inflammatory biomarkers including IL-6 and hepatocyte growth factor , An interesting study demonstrated that splenectomy in obese mice led to a decrease in IR and reduced growth of adipose tissue, However, in a contrasting study, splenectomy of obese mice resulted in facilitated progression of NAFLD , It is thus difficult to ascertain whether the spleen serves in a protective or antagonistic capacity in regards to NAFLD progression, Nevertheless, the literature suggests that splenic volume is affected by NAFLD and these changes could be used as an ancillary method for diagnosing NAFLD [124]. Finally, gut microbiota dysbiosis may play a significant role in NAFLD, Although many studies identifying NAFLD-related gut microbiota abnormalities have been performed in mice, key human studies have shown that gut dysbiosis is apparent in NAFLD patients, A study in obese juvenile patients

with NAFLD showed that Gammaproteobacteria and Prevotella were at increased concentrations compared to obese juvenile patients without NAFLD, Moreover, the microbiome changes as NAFLD progresses and research shows that increases in Proteobacteria and decreases in Firmicutes can accompany NAFLD progression [125]. Additionally, patients with NASH exhibit altered concentrations of Prevotella copri and Bacteriodes vulgatus when compared with individuals without NASH [126]. Bacteriodes concentration showed a positive link with NASH severity, while Prevotella was decreased in patients with NASH , As the severity of fibrotic lesions in NASH patients increased, the concentrations of Bacteriodes and Ruminococcus increased while Prevotella decreased. Furthermore, when patients were stratified into three groups by Ruminococcus concentration, it was observed that those with the highest concentration of Ruminococcus exhibited twice as much fibrosis as those in the bottom two groups [127]. Interestingly, microbiota modulation including the administration of probiotics enriched with Lactobacillus casei decreased inflammation and improved hepatic metabolism in a murine model [128]. Antibiotic treatment has also been shown to decrease bacterial overgrowth and stem NAFLD progression. However, antibiotic side effects must be carefully weighed and any usage of antibiotics to target microbiome dysfunction needs more research and clarification , It is clear that gut dysbiosis may contribute to and enhance poor outcomes in NAFLD patients , However, gut microbiota composition can vary among population groups and among different stages of NAFLD, making any conclusive or causational claims about gut microbiota categorization in NAFLD patients challenging , Nevertheless, some hypotheses on the ways dysbiosis can directly affect liver functioning have been developed,While NAFLD is independent of exogenous alcohol consumption, bacteria in the gut have been known to produce alcohol through ethanol fermentation, Alcohol is known to adversely affect hepatic function and several studies have shown how obese patients with NASH often exhibit an elevated blood-alcohol content (BAC) when compared to obese patients without NASH. This suggests that gut bacteria can exacerbate NAFLD progression by way of direct ethanol production , Other mechanisms through which dysbiosis can directly impact hepatic function is through the migration of bacteria directly into the liver through enhanced small intestine permeability, which is increased in patients with NAFLD [129]. Bacteria that migrate to the liver secrete proinflammatory toxins that can trigger hepatic damage, However, it is not clear if gut permeability is a cause or effect of NAFLD-related dysbiosis, The primary risk factors of NAFLD are obesity, type II diabetes, and the metabolic syndrome including dyslipidemia and hypertension ,However, diseases other than the metabolic syndrome can be associated with hepatic fat, and these might enter into the differential diagnosis of fatty liver disease of usual type, Some of these have specific clinical and pathologic features that make their distinction from NAFLD straightforward, but others are infrequent and easily overlooked [130].

CONCLUSION

1. Non-alcoholic fatty liver disease (NAFLD) is the term for a range of conditions caused by a build-up of fat in the liver.
2. It's usually seen in people who are overweight or obese.
3. Early-stage NAFLD does not usually cause any harm, but it can lead to serious liver damage, including cirrhosis, if it gets worse.

RECOMMENDATION

to prevent accumulation of fats in the liver

1-Stay at a healthy weight.

2-Exercise regularly.

3-Limit alcohol consumption.

4-Take medications as prescribed.

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