

ARTICLE

**The Association of Non Viral Liver Diseases from NAFLD to NASH to HCC with the Pandemic of Obesity, Type 2 Diabetes, or Diabesity & Metabolic Syndrome Etiopathogenetic Correlation along with Utilization for Diagnostic & Therapeutic Purposes-A Systematic Review**

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ABSTRACT

Earlier we have been reviewing the etiopathogenesis (EP) of obesity, type2 Diabetes mellitus (T2DM), Metabolic Syndrome (MetS), Non Alcoholic Fatty Acid Liver Disease (NAFLD) non alcoholic steatohepatitis (NASH), along with its propagation to Hepatocellular carcinoma (HCC) in addition to their therapies exhaustively. T2DM continues to be a major health issue with reaching epidemic to pandemic proportions. Liver disease includes a spectrum of liver injury varying from isolated steatosis known as Non Alcoholic Fatty Acid Liver Disease (NAFLD) to HCC. Clinically it has been observed that the coexistence of NAFLD as well as T2DM is prevalent. T2DM aids in the biological events that results in escalation of robustness of NAFLD that constitutes the primary etiology of chronic liver diseases. In the past 2 decades the incidence of nonviral NAFLD/NASH, obtained HCC has been escalating at a fast pace. In view of no appropriate agents for therapy of NAFLD/NASH, a thiazolidenedione group of drug pioglitazone used for T2DM therapy is utilized occasionally. Thus here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review libraryutilizingtheMeSHterms like T2DM; MetS; NAFLD; NASH; HCC; WAT; BAT; VisceralAT; Obesity; BMI; Adipocytokines; adiponectin; leptin; resistin; visfatin; irisin; Hepatokines; angiopoietin like protein 2; hepatossain; retinol binding protein 4; treatment like pioglitazone; liraglutide; elafibranor CVC (cervicroc); obeticholic acid; aramchol; selonsertib; simtuzumab; Oxidative stress(OS); insulin resistance (IR) from 1980's to 2021 till date. We found a total of 1050 articles out of which we selected 236 articles for this review. No meta-analysis was done. Hence diagnosis avoidance in addition to treatment of the generation as well as propagation of NAFLD/NASH are significant areas needing tackling. Thus here we have summarized the EP of NAFLD/NASH, as well as NAFLD/NASH, obtained HCC along with the present advantageous therapies under trial, for NAFLD/NASH. Moreover how adipocyte obtained adipokines along with liver obtained hepatokines might work as both diagnostic in addition to therapeutic targets from NAFLD to HCC.

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## 1. Introduction

Earlier we have been reviewing the etiopathogenesis (EP) of obesity, type2 Diabetes mellitus (T2DM), Metabolic Syndrome (MetS), Non Alcoholic Fatty Acid Liver Disease (NAFLD) non alcoholic steatohepatitis (NASH), along with its propagation to Hepatocellular carcinoma (HCC) in addition to their therapies exhaustively [1-24] [besides many more]. T2DM, altogether with obesity, NAFLD represents the commonest liver disease, associated -in about 30% of the general population [25]. The properties of NAFLD are hepatic triglycerides (TG), collection in addition to insulin resistance (IR) [26]. This is basically the hepatic presentation of Metabolic Syndrome (MetS) along with spans a problem encompassing benign with hepatic steatosis to NASH [27]. Widely the 2 are clubbed as Non Alcoholic Fatty Acid Liver (NAFL) as well as NASH [28]. NAFL represents isolated steatosis, whereas NASH possesses properties of steatosis, lobular inflammation (alias infiltration by inflammatory cells), hepatocellular ballooning in the existence or absence of fibrosis [29]. NASH is the one having maximum aggressiveness of the NAFLD, possesses capacity of propagation to continuous fibrosis, with a direct correlation with the risk of Hepatocellular carcinoma (HCC) generation that might be a major reason for morbidity as well as mortality stimulated by liver failure (Figure 1) [25,30]. Prevalence of NASH is about 30% in case of patients with NAFLD [31]. Roughly 20% of

patients with NASH having fibrosis propagate to cirrhosis [32]. Liver cirrhosis exists in just 50% of NAFLD-associated HCC [33]. Incidence of NAFLD-associated HCC without cirrhosis is about 8% of total HCC patients [34], while total incidence rate of HCC in NAFLD as well as NASH varies from 2-13% [35].

In the clinical scenario NAFLD is present along with T2DM, obesity, influencing synergism action resulting in greater robust liver failures [36]. Prevalence of NAFLD is thought to be about 75% in cases with T2DM along with 90% in obese cases, that point to a significant association of NAFLD with T2DM along with obesity [37]. NAFLD participates significantly in escalated incidence of T2DM in addition to its complications [28]. Further T2DM exacerbates NAFLD as well to a more robust type of NASH, fibrosis as well as HCC (Figure 1) [37,38].

HCC, represents a highly aggressive cancers [39]. Earlier hepatitis C virus was believed to the commonest etiology of HCC [40], although recently it has been illustrated that till 50% of new onset HCC cases did not have a viral etiology [41]. The causation of NAFLD/NASH stimulated HCC is highly complicated, which is correlated with a lot of modes like cellular plasticity, inflammation, apoptosis, cell cycle as well as cell demise [42]. Hence therapy of HCC is tough. Moreover it is essential that concentration is done for avoidance of NAFLD/NASH propagation by treating them earlier as well as avoidance of its propagation towards irreversible chronic liver Diseases like cir-

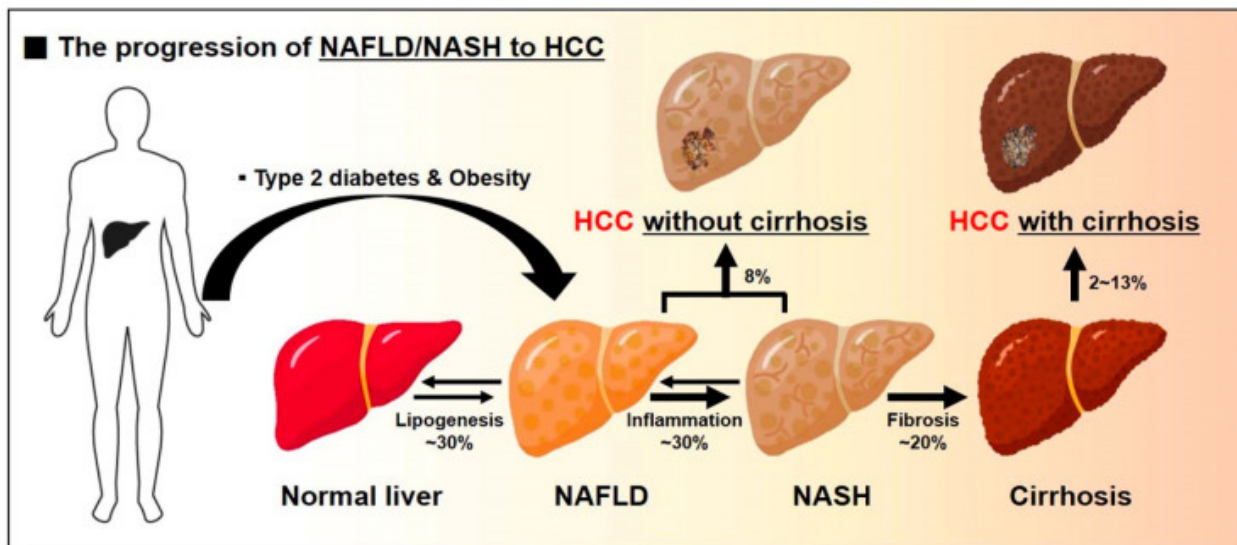


Figure 1. The progression of NAFLD/NASH to HCC

Legend for Figure 1

Courtesy ref no-30-Type 2 diabetes and obesity aggravate the progression of NAFLD/NASH to HCC. Clinically, type 2 diabetes coexists with NAFLD, and it aggravates NAFLD to more severe forms of NASH, hepatocirrhosis, and HCC, leading to a metabolically worse phenotype.

rhosis as well as HCC. No FDA approved drugs exist till date.

Besides have reviewed a lot of therapies for NAFLD, trials under way for NAFLD/NASH therapy, we had reviewed the role of adipocytokines in obesity as well as T2DM associated heart failure (HF). Here we have tried to update on EP of NAFLD/NASH, as well as NAFLD/NASH associated HCC, besides the present beneficial therapies for NAFLD/NASH under trials. Moreover the initiation of as well as propagation can get influenced by adipokines/organokines liberated from Metabolic organs when Metabolic impairment exists like T2DM as well as obesity<sup>[43]</sup>. Thus here we have concentrated on organokines liberated by AT as well as liver. That are key organs for controlling of lipid metabolism. Newer understanding with regards to adipokines/hepatokines which might serve as potential diagnostic as well as therapeutic targets in NAFLD/NASH as well as NAFLD/NASH obtained HCC. These are believed to be biological markers which can anticipate robustness of NAFLD from NAFLD to HCC.

Thus here we carried out a systematic review on the association of various metabolic disturbances in the initiation of various liver disorders ranging from NAFLD to NASH and further towards HCC.

## 2. Methods

Thus here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like T2DM; MetS; NAFLD; NASH; HCC; WAT; BAT; VisceralAT; Obesity; BMI; Adipocytokines; adiponectin; leptin; resistin; visfatin; omentin; irisin; Hepatocytokines; angiopoietin like protein 2; hepatocytin; retinol binding protein 4; treatment like pioglitazone; liraglutide; elafibranor CVC (cervicroc); obeticholic acid; aramchol; selonosertib; simtuzumab; Oxidative stress(OS); insulin resistance (IR) from 1980's to 2021 till date.

## 3. Results

We found a total of 1050 articles out of which we selected 236 articles for this review. No meta-analysis was done.

## 4. Discussion

### 4.1 Etiopathogenesis (EP) of Non Alcoholic Fatty Acid Liver Disease (NAFLD) as well as Non Alcoholic Steatohepatitis (NASH)

Disturbed Balance -among fatty acids(FA) Metabolism

NAFLD represents the commonest cause of chronic liver disease. NAFLD occurs, secondary to escalated triglycerides (TG), collection in the liver<sup>[26]</sup>. Hence the balance among FA input as well as -output is key<sup>[44]</sup>. Implying that generation of NAFLD takes place if levels of exogenous FA uptake (by dietary ingestion along with adipose tissue (AT) lipolysis) as well as endogenous FA generation (DNL in liver is greater than the liberation of FA (FA oxidation, lipolysis, as well as FA liberation in very low density lipoprotein (VLDL) TG) from liver (Figure 2).

The liberation of FA from AT as well as effectiveness of FA uptake by liver are escalated by about 59% in cases of NAFLD<sup>[45]</sup>. Liver FA is based on the number as well as action of specific FA transporter as well as FA carrier proteins like FA translocase (FAT, CD36), FA transport polypeptide [FATP] as well as, fatty acids binding protein (FABP)<sup>[46]</sup>. Like hepatic expression of FAT/CD36 is significantly escalated in cases with NAFLD, as well as hepatic expression of FABP4 as well as FABP5 is intricately correlated with intrahepatic TG collection.

In about 26% of patients, the method of aiding liver FA pool is hepatic Denovo lipogenesis (DNL)<sup>[47]</sup>. DNL represents metabolic event which is implicated in generation of new FA from escalated glucose<sup>[48]</sup>. It significantly aids in hepatic lipid collection in etiopathogenesis of NAFLD<sup>[48]</sup>. The activation of 2 Transcription factors (of sterol regulatory element binding protein 1c (SREBP1c), as well as carbohydrate responsive element binding protein [ChREBP]), enhanced by insulin as well as glucose reaction to dietary carbohydrate<sup>[49]</sup>. They possess synergistic significant part in coordinated control of hepatic DNL. In rest 15% of patients of NAFLD, FA pool is obtained from diet TG. That is correlated with chylomicron<sup>[45]</sup>.

The maximum lucrative theory in etiopathogenesis of NAFLD is "2hit" posit<sup>[50]</sup>. 1st hit is IR, secondary to escalated FA flux, 2<sup>ND</sup> is inflammation, correlated with gut obtained endotoxins, Oxidative stress (OS) as well as mitochondrial impair. It is intricately associated with NAFLD-NASH.

### Endotoxin behavior

NAFLD as well as other insulin resistance (IR) disease are correlated with activation of innate immune system=>chronic inflammation<sup>[51]</sup>. Recently gut obtained endotoxin, like lipopolysaccharides (LPS) have been posited to possess a key part in liver inflammation secondary as well as propagation to chronic Liver Disease<sup>[52]</sup>. Normally, Endotoxin can get absorbed from the lumen of the intestine into the portal venous system in addition to absorbed endotoxin would get cleared fast by the reticulo endothelial system, specifically kupffer cells<sup>[53]</sup>. Never-

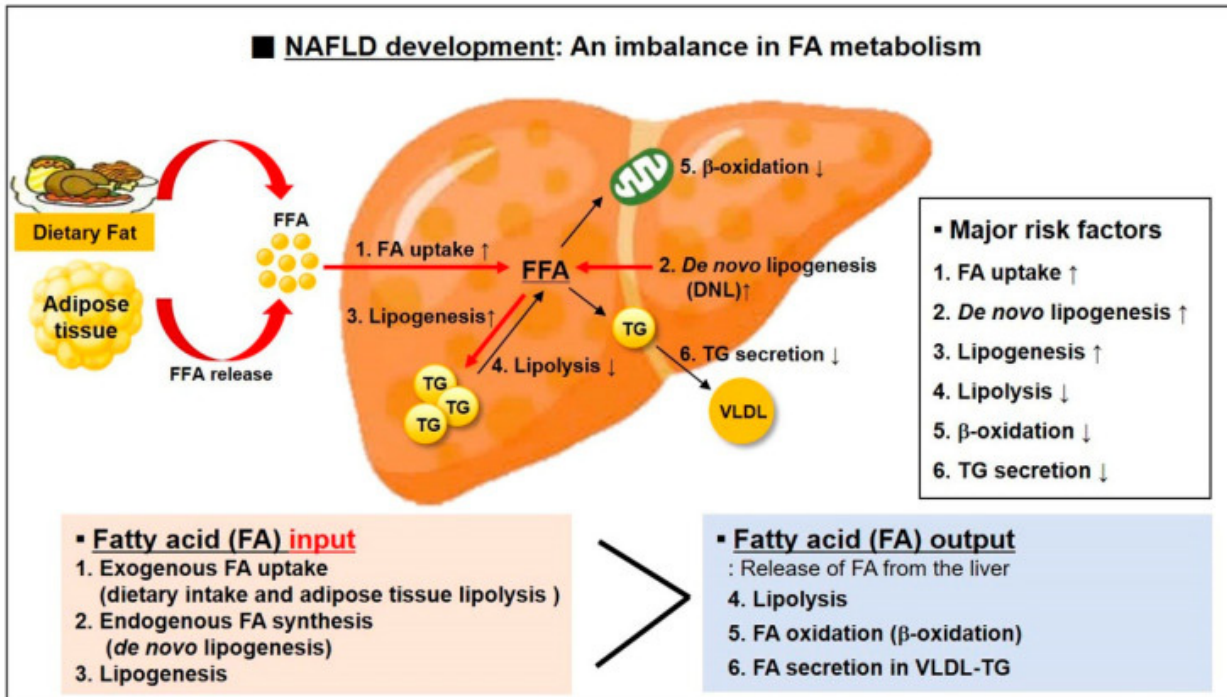


Figure 2. NAFLD development: An imbalance in FA metabolism

Legend for Figure 2

Courtesy ref no-30-NAFLD development is caused by an imbalance in the intrahepatocellular fatty acid (FA) metabolism. Hepatic TG accumulation is promoted when the FA input is greater than the FA output in the liver. The greater part of FA taken up by liver is mainly derived from the lipolysis of subcutaneous adipose tissue TG. Another major source of FA in the liver is derived from *de novo* lipogenesis that converts excess glucose into FAs. On the other hand, the consumption of FA is possible through the signaling pathway involved in lipolysis, β-oxidation, and TG secretion (→: signaling pathways related with TG accumulation by FA, ←: signaling pathways related with the consumption of FA).

theless, obesity, type2 Diabetes mellitus (DM) along with other nutritional parameters can change intestinal permeability as far as bacterial excessive growth leading to amucosal barrier that becomes leaky resulting in bacterial transportation, that points to the liberation of endotoxin into the systemic circulation<sup>[54]</sup>. These invasive pathogenic deleterious by products have an impact on the liver lipid collection along with acceleration of proinflammatory in addition to fibrosis events<sup>[53]</sup>.

The part of LPS from gut microbiota (GM) in the generation of NAFLD as well as NASH has been highlighted<sup>[54]</sup>. Circulating LPS amounts small intestinal permeability, along with bacterial excessive growth are escalated in cases of NAFLD, with these factors being correlated with the robustness of hepatic steatosis<sup>[54,56]</sup>. Livers getting blood directly from the portal vein remain the major targets of LPS, alias endotoxin, with LPS toll like receptor 4 (TLR4) being one of the key pathways for the generation of NAFLD. In case of mouse models, LPS infusion causes stimulation of hepatic steatosis in addition to hepatic insulin resistance, along with hepatic weight escalation

<sup>[57]</sup>. LPS results in acceleration of liver damage in mice receiving a diet lacking methionine-choline<sup>[58]</sup>. The LPS binding protein LBP-CD14 complex results in stimulation of TLR4, that is necessary cascade needed for inflammatory propagation<sup>[59]</sup>. Once LBP deletion occurs it ameliorates inflammation modulated liver damage<sup>[60]</sup>. TLR4 possesses the characteristics of stimulation of nuclear factor κB (NFκB) in addition to liberation of proinflammatory cytokines like interleukin-1β (IL-1β), Tumor necrosis factor alpha (TNFα) as well as IL-6<sup>[61]</sup>. Further it has the ability of recalling damage associated molecular patterns (DAMP), which get liberated from damaged cells, as well as modulates FA-stimulated inflammation<sup>[51,62]</sup>. In the form of -Pharmacological treatments in NAFLD as well as NASH which target the microbiome, IMM-24 (an anti-LPS antibody), solithromycin (next generation macrolide antibiotic) along with TLR4 antagonist<sup>[63]</sup>.

### Oxidative stress

Chronic Oxidative stress (OS) is crucial modes resulting in liver damage in NAFLD. Oxidative stress is a



process occurring generally in NAFLD as well as NASH secondary to escalated generation of Reactive oxygen species (ROS) [64]. ROS in addition to lipid peroxidation can reason out maximum histological parameters of NAFLD as well as NASH [65]. In case of hepatic steatosis patients, mitochondrial ROS Oxidizes hepatic fat deposits along with ROS stimulated Fas ligand expression can generate apoptosis [65]. Both peroxidation of along with intra cellular membrane can directly result in apoptosis stimulation as well as necrosis [65]. The robustness of lipid peroxidation is associated with the robustness of steatosis in addition to can reason out the correlation among the robustness of steatosis in addition to the chances of necrosis inflammation along with fibrosis in NASH [66]. ROS that is a critical factor in the etiopathogenesis of NASH, can result in a self created cycle of lipid peroxidation as well as further cause ROS generation [67]. Alteration of -mitochondrial DNA can result secondary to products generated by lipid peroxidation as well as result in stimulation of the transcription factor nuclear factor  $\kappa$ B (NF $\kappa$ B), which causes upregulation of TNF $\alpha$  [68]. Hence it further aids in dysfunctional mitochondrial respiration in addition to escalation of ROS generation [68].

Escalation of mitochondrial  $\beta$ -oxidation of FFA is a significant generator of ROS in NAFLD as well as NASH [69]. Enhancement of FFA flux during early NAFLD stage cause activation of mitochondrial FA-oxidation (FAO), which points to an early liver compensation modes for hampering liver fat collection along with sustenance of liver lipid homeostasis [26]. In case of NAFLD as well as NASH mitochondrial FAO is further escalated or minimum conserves in the form of a compensation reaction. The disturbed balance among mitochondrial FAO as well as electron transport chain (ETC) would aid in escalation of ROS generation by escalated leaking of electrons from the ETC [26,69]. ROS stimulated lipid per oxidation results in inflammation along with hepatic fibrogenesis via the stimulation of hepatic stellate cells (HSC's) [70].

Trusted circulation markers which might point OS in cases with NAFLD have got documented. Urinary 8-iso prostaglandin F $2\alpha$  (8-isoPGF $2\alpha$ ) is believed to be trusted pointer of OS in vivo [71], as well as soluble NOX2-obtained peptide (s-NOX2-dp) are further agreed upon as marker that is correlated with ROS production on stimulation of NOX2, that is a member of NADPH-oxidase family [72]. Enhancement of urinary amounts of 8-iso-PGF $2\alpha$  as well as serum soluble NOX2-obtained peptide are believed to be [73] trusted pointers of oxidative stress in case of chronic inflammation along with metabolic disease [73]. Further the utilization of these markers can be done for OS regarding anticipation of robustness of liver

injury in NAFLD [74]. LPS is a significant constituent of outer membrane of gram negative bacteria which results in stimulation of exacerbation of inflammation as well as Oxidative stress [75]. Enhancement of circulating amounts of NOX2 as well as LPS in NAFLD point to a potential part in gut obtained LPS in systemic NOX2 stimulation [76]. Moreover -s- NOX2-dp -amounts -possess a positive correlation of histological grading with steatosis, inflammation, ballooning, fibrosis as well as NAFLD activity score (NAS) [76]. Gut obtained LPS might result in activation of TLR4, as well as TLR4 – modulated NOXs activation can lead to generation of ROS by macrophage infiltration [77]. This can aid to hepatic steatosis in addition to IR [77].

Nevertheless, the variability of metabolic alterations take place in NAFLD are not enough to get reasoned out by “2 hit” posit. Maximum metabolic conditions like obesity, T2DM, Metabolic Syndrome (MetS), dyslipidemia work as the risk factors for generation of NAFLD by the “multiple hits” implicating a lot of factors (Figure 3) [78]. These “multiple hits” are bioactive molecules liberated from AT, nutritional factors as well as environmental factors [78].

## 4.2 Attractive Treatment in NAFLD as well as NASH

With the recently advocated that pioglitazone, along with high dosages of Vitamin E, efficaciously result in amelioration of escalation of histological alterations in cases of NASH [79]. Conversely metformin has no such action in NAFLD patients [80], as well as ursodeoxycholic acid (UDCA), has no influence on liver histological alterations, inflammation, or fibrosis in patients with NASH [82]. Following are certain Pharmacological examples under Clinical trials as well as might work out as promising agent for NASH treatment (Figure 4). In addition, the metabolic profile along with liver histology correlated effectiveness of these attractive drugs [19,20,81].

### Pioglitazone

Pioglitazone represents an anti diabetic drug thiazolidenediones (TZD) class utilized for T2D treatment [83]. TZD'S are further referred to as glitazones. Two TZD's are presently approved by FDA for monotherapy or combination treatment with metformin as well as sulfonylureas for T2D treatment [84]. TZD's meant for insulin sensitization aid in controlling glycemia along with insulin resistance (IR) [84]. The maximum significant benefit of TZD's was that hypoglycemia doesn't result secondary to its utilization with single treatment, with it not being contraindicated in patients presenting with renal disease [85].

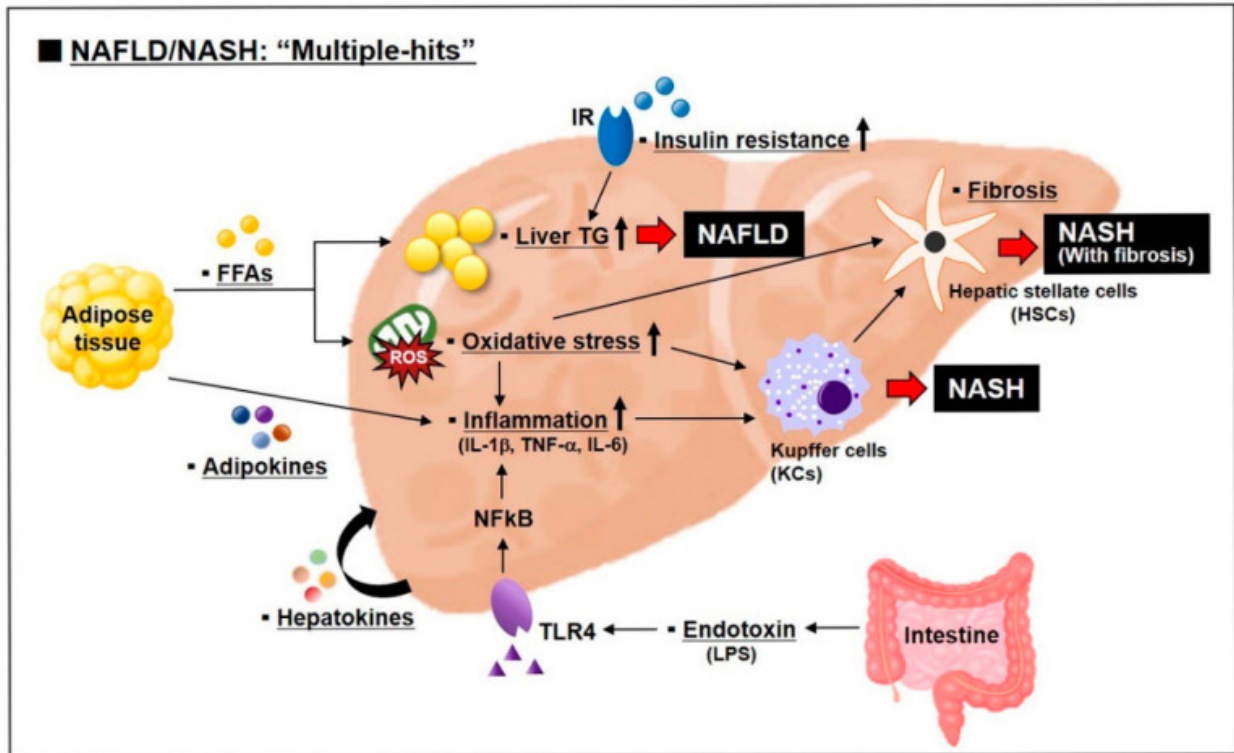


Figure 3. NAFLD/NASH: "Multiple-hits"

Legend for Figure 3

Courtesy ref no-30-Multiple-hits pathogenesis of NAFLD and NASH. NAFLD begins with hepatic lipid accumulation and insulin resistance, and progresses to NASH with the concert of various factors such as inflammation, endotoxin, organokines (adipokines and hepatokines), and oxidative stress. (\*: Factors related with multiple-hits).

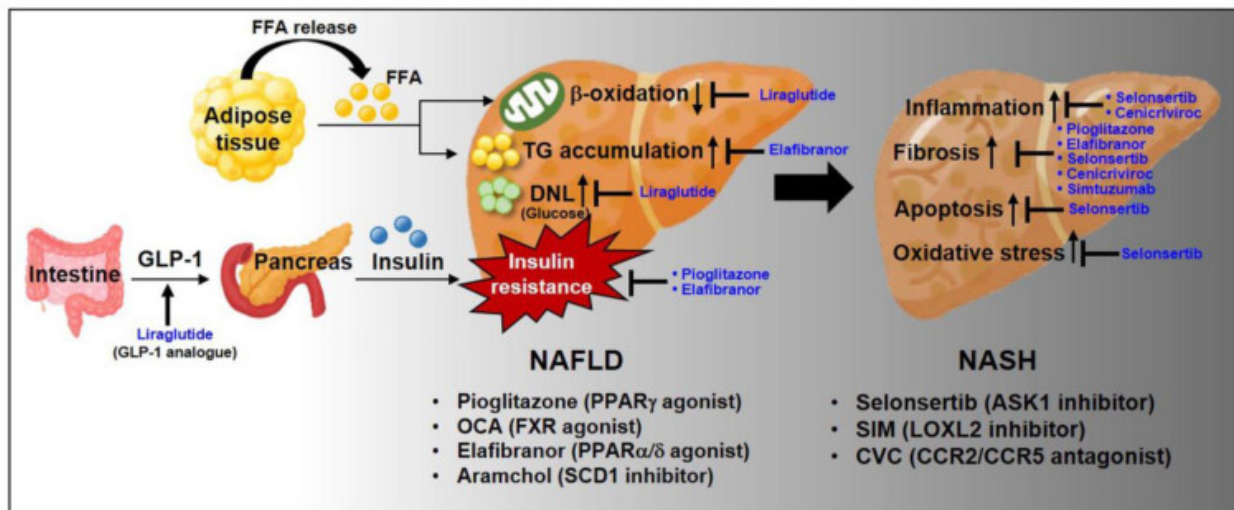


Figure 4. Pharmacological examples

Legend for Figure 4

Courtesy ref no-30-Current therapeutic targets for pharmacological treatment of NAFLD and NASH. There are no FDA-approved medications for patients with NAFLD/NASH so far. Currently, various pharmacological therapeutic candidates are being applied to the clinical trials. The illustration demonstrates the targeted pathway and phenotype for treatment of patients with NAFLD and NASH.

TZD's work by controlling metabolic pathway by binding to the nuclear transcription factor Peroxisome Proliferator adenine Activated Receptor  $\gamma$  (PPAR  $\gamma$ ) in addition to modulation of the expression of the target genes<sup>[86]</sup>. The genes possess a part in controlling glucose metabolism, storage of FA's along with adipocytes differentiation<sup>[87]</sup>. In agreement with this PPAR  $\gamma$  agonist escalated the expression of glucose transporter 4 (GLUT4 alias SLC2A4) as well as translocation, hamper TNF $\alpha$  as well as result in enhancement of insulin sensitivity in case of organs which are insulin sensitive<sup>[88]</sup>. Conversely T2D treatment effects increments of weight as an adverse action, since PPAR  $\gamma$  Receptor's are markedly expressed in adipocytes<sup>[89]</sup>. Enhancement of fat mass is restricted to the subcutaneous adipose depots instead of the visceral area<sup>[88,90]</sup>. That can be prevented by metformin therapy<sup>[91]</sup>.

Recently it got documented that the PPAR  $\gamma$  agonist Pioglitazone possesses significant actions on NAFLD/NASH patients. In case of patients with NASH, it ameliorated liver fat collection along with fibrosis<sup>[92]</sup>. In case of patients with NASH in addition to T2DM, it results in reduction of hepatic steatosis, inflammation as well as serum alanine amino transferase (ALT) as well as aspartate amino transferase (AST) with better liver function<sup>[93]</sup>. In rodent models it decreases hepatic gluconeogenesis along with results in escalation of insulin sensitivity in the liver as well as other peripheral tissues<sup>[94]</sup>.

### **Obeticholic acid (OCA); or INT-747; Farnesoid X receptor [FXR] agonist**

Obeticholic acid (OCA) represents a Farnesoid X receptor [FXR] agonist, that is a nuclear receptor, with significant expression in the liver along with small intestine, having a significant part in the generation in addition to enterohepatic circulation of bile acids, besides controlling hepatic glucose as well as lipid metabolism, inflammation as well as lipoprotein constituents in addition to bile acid generation<sup>[95]</sup>. In rodent models OCA has anti-inflammatory along with, anti-fibrotic actions on HSC's as well as macrophages<sup>[96]</sup>. The transcriptional repressor small or short heterodimer partner (SHP), crossreacts with liver receptor homolog 1 (LRH1), that represents a positive controller of CYP7A1 which encodes for the rate limiting enzyme in the classic bile acids generation pathway as well as represses its ability for transcription<sup>[97]</sup>. HSC's getting exposed to FXR ligands escalated the expression of the transcriptional repressor SHP along with reduction of factors correlated with liver fibrosis<sup>[96]</sup>. Belief is that an FXR SHP controlling axis has a significant part in controlling liver fibrosis. OCA stimulation of FXR-action has 100 times greater potency in contrast to the chenode-

oxycholic acid, that is a natural FXR agonist<sup>[98]</sup>. Escalation of insulin sensitivity results with the use of OCA in addition to, reduction of hepatic inflammation markers as well as fibrosis in patients with T2D as well as NAFLD<sup>[99]</sup>. Weight reduction results in patients with NASH, with this weight reduction having extra advantageous actions on Serum ALT/AST amounts along with liver histology<sup>[100]</sup>. In addition to that it results in significant enhances fibrosis in patients with NASH<sup>[101]</sup>. It represents 1 of the agents holding maximum promise for NASH therapy, is in phase 3 trials<sup>[102]</sup>.

### **Elafibranor (GFT-505; Peroxisome Proliferator Activated Receptor (PPAR)-agonist)**

PPAR's represent transcription factors that get activated by ligand, belonging to the nuclear hormone receptors superfamily<sup>[103]</sup>. Their expression occurs in liver, adipose tissue (AT), heart, skeletal muscle, as well as kidney, besides controlling  $\beta$ -oxidation along with gluconeogenesis<sup>[102]</sup>. Three kinds of nuclear receptor isoforms exist; PPAR $\alpha$ , PPAR  $\delta$ , as well as PPAR $\gamma$ . PPAR $\alpha$ , facilitates  $\beta$ -oxidation, decreases triglycerides (TG), amounts, besides escalated high density lipoprotein (HDL) cholesterol amounts<sup>[104]</sup>. Further it hampers nuclear factor  $\kappa$ B (NF $\kappa$ B) stimulation of inflammatory genes<sup>[104]</sup>. PPAR $\alpha$  agonists like fibric acids derived compounds like fibrates is in usage widely for the treatment of hypertriglyceridemia, while it doesn't possess significant actions in NAFLD patients<sup>[105]</sup>. The reason for this is the existence of PPAR $\alpha$  in a lot of organs besides liver. Akin to PPAR $\alpha$ , PPAR  $\delta$  causes escalation of FA oxidation along with decreases macrophages in addition to Kupffer cells activation, in view of its existence on macrophages<sup>[106]</sup>. GW50516 represents a synthetic PPAR  $\delta$  particular agonist<sup>[107]</sup>. GW50516 can be thought of as attractive proposition in Clinical trials, in view of it possessing potent efficiency, however it possesses safety issues<sup>[108]</sup>.

Elafibranor, alias GFT505 is a double PPAR $\alpha$  as well as  $\delta$  agonist<sup>[109]</sup>. It attenuates inflammation, apoptosis, necroptosis in case of NASH mouse model<sup>[110]</sup>. It led to reduction of histological hepatic steatosis, inflammation in addition to, robustness of fibrosis in both the NAFLD/NASH as well as fibrosis mouse model<sup>[111]</sup>. It has a tendency to result in weight reduction, but not that of liver in case of diet stimulated NAFLD/NASH rodent models<sup>[112]</sup>. In cases of obese subjects it enhances hepatic as well as peripheral insulin sensitivity<sup>[113]</sup>. Moreover it hampers proinflammatory (interleukin-1 $\beta$ , TNF $\alpha$  as well as F4/80), in addition to, profibrotic transforming growth factor beta TGF- $\beta$ , tissue inhibitors of matrix metalloproteinase (TIMP2), collagen type1, alpha2 as well as collagen



type1, alpha2 markers in obese subjects<sup>[114]</sup>. No -weight gain was reported<sup>[109,115]</sup>. Presently it is getting analysed in phase 3 trials in NASH subjects<sup>[102]</sup>.

### **Arachidylamido cholanoic acid (Aramchol) Stearoyl-Co A Desaturase (SCD1) Inhibitor**

Aramchol represents the liver targeted, an innovative synthetic lipid molecule, a conjugate of the bile acid, cholic acid as well as arachidic acid (FABACs). It influences liver fat metabolism by causing reduction in FA generation along with escalation of  $\beta$ -oxidation<sup>[117]</sup>. Furthermore it results in stimulation of cholesterol efflux by activation of the ATP – binding cassette transporter A1 (ABCA1)<sup>[118]</sup>. Additionally, it decreases inflammation as well as fibrosis in methionine as well as choline deficient (MCD) fed mice<sup>[116]</sup>. Moreover it tends to ameliorate steatohepatitis as well as fibrosis by causing reduction in SCD1 amounts by controlling the transsulfuration pathway resulting in escalated glutathione amounts as well as the glutathione disulfide (GSSH/GDX redox couple for appropriate balance of redox environment<sup>[116]</sup>.

In a phase 2 trial, of patients with NAFLD, Aramchol decreased the liver fat amounts along with liver histology<sup>[119]</sup>. No significant toxicity was observed as seen in circulating ALT as well as AST amounts, besides alkaline phosphatase (AP) amounts<sup>[119]</sup>. In view of it targeting general properties of NASH (like escalated liver fat amounts, lipotoxicity as well as OS) in addition to fibrosis Aramchol is at present getting generated for NASH treatment along with that of fibrosis. No significant alterations in body weight was observed in NASH patients. Phase 3 clinical trials are ongoing in patients with NASH as well as fibroses got started in 2019.

### **Liraglutide (GLP-1 Agonist)**

Glucagon like peptide 1 receptor (GLP-1) agonists have got well proven -in the form of attractive anti Diabetic agent in animals as well as - patients with T2DM<sup>[120]</sup>. GLP-1 represents an incretin hormone liberated from the L-cells in the distal ileum along with colon<sup>[121]</sup>. It causes stimulation of pancreas resulting in insulin generation, in addition to decreases glucagon generation<sup>[122]</sup>. Endogenous GLP-1 gets broken down by Dipeptidyl Peptidase-4 (DPP-4) enzyme within few minutes whereas Liraglutide possesses long half life 13h<sup>[123]</sup>.

Exenatide that is a synthetic Extendin-4 was the 1<sup>st</sup> GLP-1R agonist that got FDA approval in 2005 for T2DM treatment in form of monotherapy or as add on therapy with metformin as well as or sulfonyl urea, in case control was not sufficient<sup>[124]</sup>.

Liraglutide, the second GLP-1R agonist that got a license in 2010 by FDA for T2DM treatment. Further in 2020 it got FDA approval for therapy of obesity patients, dependent on its weight reduction advantages<sup>[125]</sup>. It possesses cardiovascular safety while treatment for weight reduction<sup>[126]</sup>. Anorexia secondary to Liraglutide is associated with glutamatergic POMC neurons, resulting in weight reduction<sup>[127]</sup>. In cases of NAFLD as well as NASH it causes reduction in liver fat amounts, besides with liver histology getting rectified along with normalization of enzymes (ALT as well as AST amounts) without deterioration of fibrosis<sup>[128]</sup>. In view of rodent studies demonstrating Liraglutide conferred protection to pancreatic  $\beta$  cells from apoptosis via AKT modulated survival signaling<sup>[129]</sup>. It enhanced insulin sensitivity by activation of adenine monophosphate activated -protein kinase (AMPK) as well as decreases hepatic steatosis by modulation of lipid transportation,  $\beta$ -oxidation, DNL, as well as autophagy<sup>[130]</sup>.

### **Selonsertib (ASK1 Inhibitor)**

Ballooning of hepatocytes, points towards the stimulation of the apoptosis pathway, which represents a hallmark of NASH along with fibrosis propagation<sup>[131]</sup>. Selonsertib represents -1<sup>st</sup> in class Inhibitor of the apoptosis signal regulating kinase 1 (ASK1)<sup>[132]</sup>. Selonsertib hampers phosphorylation as well as activation of ASK1 by binding to the catalytic kinase domain of ASK1. It has been posited recently possessing therapeutic potential for fibrotic Diseases. In case of murine models, ASK1, that is a serine/threonine kinase, results in phosphorylation of p38 mitogen activated protein kinase (MAPK) as well as, resulting in activation of c-Jun –N terminal kinase (JNK) resulting in activation of stress response pathways which exacerbate hepatic inflammation, apoptosis in addition to fibrosis<sup>[133]</sup>. In murine models of NASH, it significantly enhances besides hepatic steatosis in addition to fibrosis correlated with NASH, enhancement of cholesterol, the bile acid and lipid metabolism<sup>[133]</sup>. In phase 2 Clinical trials of NASH patients as well as stage 2-3 fibrosis, it has got demonstrated to avoid inflammation, fibrosis, escalated apoptosis as well as -propagation to cirrhosis<sup>[134]</sup>. Conversely, phase 3 Clinical trials of NASH patients along with advanced fibrosis were observed to escalate liver histology, but had no influence on fibrosis regression<sup>[135]</sup>.

### **Simutuzumab (SIM;G6624)**

Simutuzumab (SIM) represents a monoclonal Ab, that targets lysyl oxidase –like 2 (LOXL2) enzymatic activity which catalyzes the crosslinking of collagen in addition to elastin, resulting in remodeling of the extra cellular ma-



trix (ECM)<sup>[136]</sup>. SIM binds TO LOXL2 as well as hampers its enzymatic action<sup>[137]</sup>. Hence it hampers the generation of growth factors that includes [connective tissue growth factor (CTGF)/CCN2] as well as TGF $\beta$ 1 in addition to results in reduction of fibrosis<sup>[138]</sup>. In a mouse model possessing advanced fibrosis stimulated by NASH, SIM possesses an extra action in combination with the ASK1 Inhibitor<sup>[134]</sup>. Nevertheless, in phase 2b clinical trials of patients presenting with advanced fibrosis secondary to NASH it did not display any action on enhancement of fibrosis or cirrhosis that had been verified by hepatic collagen amounts<sup>[139]</sup>.

### C-C chemokine receptor CCR Dual -types -2 as well as 5 (CCR2/CCR5) antagonist -(cenicriviroc)

Liver inflammation is intricately correlated with chemokines responsible for controlling migration of hepatocytes as well as immune cells<sup>[140]</sup>. The C-C chemokine receptor 2 as well as 5 (CCR2, as well as -CCR5) with their associated ligands CCL2 as well as CCL3-5) have a correlation with the pathogenesis of Liver inflammation as well as fibrosis in the generation of<sup>[140,141]</sup>. CCR2 in addition to its ligand CCL2 escalated hepatic steatosis, macrophages collection, inflammation along with fibrosis<sup>[140]</sup>. Hepatic Stellate cells (HSCs) on activation, aid in fibrosis, liberate CCL5. CCL5 influences profibrotic action in hepatocytes through its receptor CCR5 as well as results in stimulation of lipid collection as well as proinflammatory factors<sup>[141]</sup>.

CVC or cenicriviroc represents an innovative CCR2, as well as CCR5 antagonist which is at present in Clinical generation for the therapy of liver fibrosis patients presenting with NASH<sup>[142]</sup>. CVC results in reduction of markers of inflammation like IL-1 $\beta$ , IL-6 as well as influences antifibrotic actions<sup>[142]</sup>. Fast track movement was given by FDA in 2015, being a highly lucrative therapy for NASH as well as liver fibrosis. In a phase 2b study of NASH patients presenting with stage 2-3 fibrosis, CVC -demonstrated enhancement in liver fibrosis. In addition to no deterioration in -NASH<sup>[143]</sup>. At present a phase 3 clinical trial is ongoing for the therapy of NASH cases with liver fibrosis<sup>[144]</sup>.

### 4.3 Diagnostic Approaches as well as Therapeutic Targets in NAFLD as well as - NASH – Adipocytokines

It is thought that NAFLD as well as NASH are secondary to lots of etiopathogenetic factors<sup>[78]</sup>. Of these we concentrate on adipokines liberated from adipose tissue (AT) which yield fatty acids (FA) as the main site aid-

ing for NAFLD generation<sup>[45]</sup>. Various Adipokines are implicated in the pathogenesis as well as propagation of NAFLD<sup>[145]</sup>. Leptin, resistin, in addition to visfatin have a part in NAFLD generation as well as propagation of NASH<sup>[145,147]</sup>. Conversely adiponectin, irisin as well as ghrelin have advantageous actions on NAFLD as well as NASH<sup>[148,149]</sup>. Pharmacological drugs which impact liver histology along with pathophysiology might affect these adipocytokines amount. This points that adipocytokines could prove to be significant therapeutic targets as well as biomarkers in NAFLD robustness anticipation (Figure 5). These adipocytokines might further have a significant role in generation of HCC.

### Adiponectin

Adiponectin is a significant Adipocytokines possessing the ability to hamper NAFLD generation. A reduction of circulating amounts of Adiponectin was found in cases of NAFLD as well as NASH<sup>[150]</sup>. They had an inverse association with the robustness of hepatic steatosis as well as inflammation. Pioglitazone, the antidiabetic which had a beneficial action on liver histology escalated adiponectin amounts, in patients with NASH<sup>[93]</sup>. Nevertheless, metformin the commonest used antidiabetic agent did not have any significant actions on either the liver histology but decreased the adiponectin amounts<sup>[89,151]</sup>. Vitamin E has a robust antioxidant action that can confer protection to bodies cells against Oxidative stress<sup>[152]</sup>. It had been thought to be an alternate medicine advocated for NAFLD as well as NASH. It enhances liver histology as well as displays certain adv actions in case of non Diabetes mellitus cases with NASH, as well as apparently it enhances adiponectin amounts<sup>[153]</sup>. Nevertheless, it has no efficacy in NASH cases with T2DM<sup>[153]</sup>. In case of mouse models, adiponectin represses hepatic lipid collection by lipid metabolism collection by escalated FA oxidation along with reduction in DNL<sup>[94]</sup>. Adiponectin has anti inflammation, anti fibrotic as well as anti apoptosis action<sup>[154]</sup>. Adiponectin delivery escalates hepatic steatosis along with inflammation<sup>[154]</sup>. Moreover adiponectin expression has an inverse association with tumor size as well as recurrence<sup>[155]</sup>.

### Leptin

Leptin is a hormone possessing appetite repression actions, that gets liberated from fat cells. It controls food consumption, body fat in addition to insulin sensitivity<sup>[156]</sup>. In animal models it is believed to escalate lipid metabolism in case of non AT's<sup>[157]</sup>. Nevertheless, in liver, it accelerates hepatic IR, that results in liver steatosis. Further it escalates -liver fibrosis<sup>[156]</sup>. Leptin delivery might

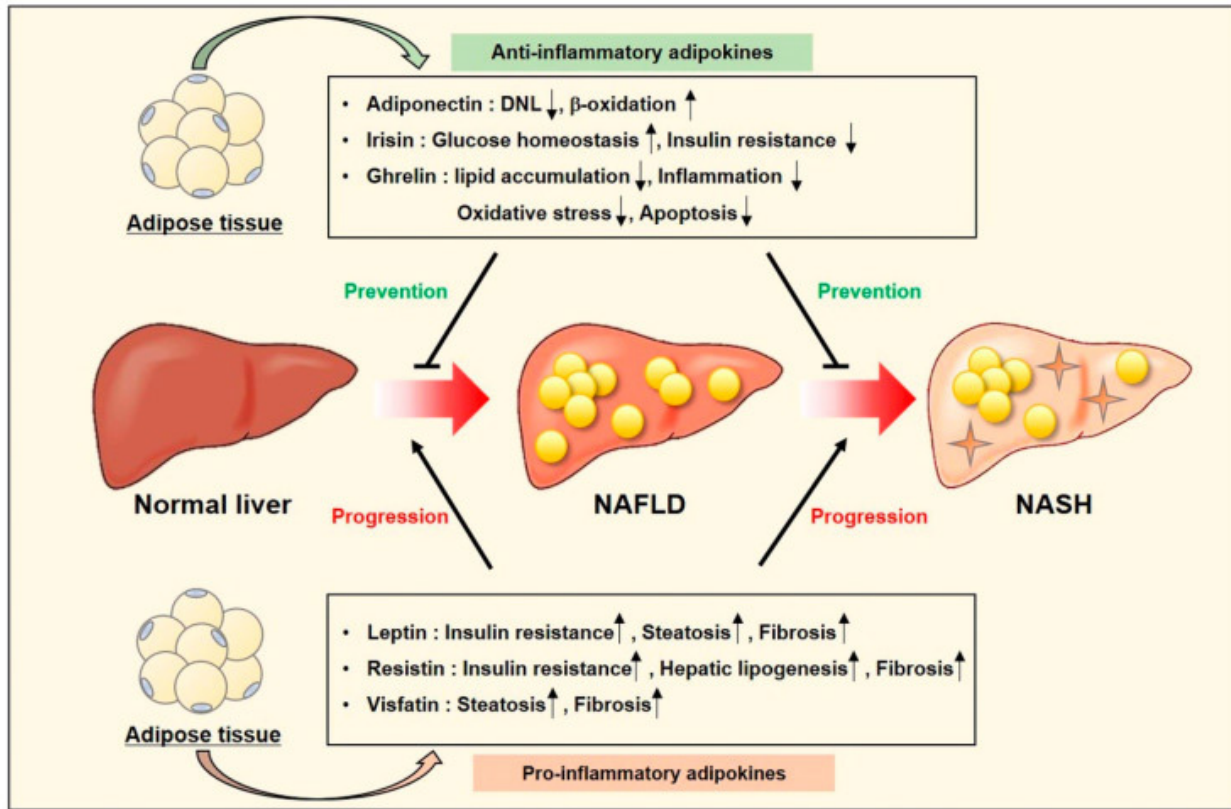


Figure 5. NAFLD robustness anticipation

Legend for Figure 5

Courtesy ref no-30-Adipokines as diagnostic markers and therapeutic targets in NAFLD and NASH. Adipokines that are secreted from adipose tissues are classified into anti-inflammatory adipokines and pro-inflammatory adipokines. Anti-inflammatory adipokines including adiponectin, irisin, and ghrelin inhibit the development and progression of NAFLD and NASH, whereas pro-inflammatory adipokines including leptin, resistin, and visfatin promote the development and progression of NAFLD and NASH.

escalate proinflammatory along with fibrogenic reaction in the liver through procollagen 1 along with transforming growth factor beta (TGF-β1)<sup>[158]</sup>. Nevertheless, in humans its actions are not certain. Escalated circulating amounts are present in patients with NASH<sup>[159]</sup>. Leptin expression has a positive association with robustness of steatosis, inflammation along with fibrosis<sup>[160]</sup>. Leptin expression has a positive association with cell proliferation in HCC, as validated by proliferation marker Ki67<sup>[133]</sup>.

### Resistin

Resistin is a proinflammatory adipocyte obtained modulator of hepatic IR<sup>[161]</sup>. Further it gets expressed in liver as well. It is correlated with hepatic lipogenesis as well as liver fibrosis<sup>[162]</sup>. Circulating Resistin amounts are escalated in patients with NAFLD as well as NASH, with circulating Resistin amounts in NAFLD patients are associated with the robustness of steatosis, inflammation along with fibrosis<sup>[162]</sup>. Escalated Resistin amounts are believed to be correlated with IR. In subjects with NAFLD Pioglitazone

therapy escalates insulin sensitivity along with reduces plasma Resistin amounts<sup>[163]</sup>.

### Ghrelin

Ghrelin represents an anti-inflammatory Adipokine. It is the endogenous ligand for growth hormone secretagogue receptor possessing a peptide structure having 28 amino acids<sup>[164]</sup>. In patients with NAFLD lesser Ghrelin are correlated with IR<sup>[165]</sup>. Plasma Ghrelin amounts possess a significant association with liver function. Nevertheless, Ghrelin amounts are not influenced by Pioglitazone in the form of one of insulin sensitizers<sup>[43]</sup>. At the time of as well as following NAFLD generation, Ghrelin delivery escalates lipid metabolism, inflammation, Oxidative stress as well as apoptosis<sup>[166]</sup>. In mouse models Ghrelin resulted in reduction in TG amounts as well as the cytokines TNF-α, IL-6 as well as ameliorated lipotoxicity via autophagy activation in addition to hampering NFκB<sup>[167]</sup>. In toto Ghrelin might work as a biomarker for both diagnosis and management of non alcoholic fatty liver disease.

## Irisin

Irisin is a myokine liberated from skeletal muscles on shivering in addition to exercise <sup>[168,169]</sup>. Fibronectin typeIII domain containing 5 precursors (FNDC5) is the precursor of Irisin. FNDC5/Irisin facilitate thermogenesis in AT via ERK as well as p38pathways <sup>[170]</sup>. It causes enhancement of glucosehomeostasis along with IR, besides resulting in weight <sup>[171]</sup> reduction. In the recent past FNDC5/Irisin induction was obtained at the time of adipocytes differentiation, as well as can get over liberated from human visceral (VAT) as well as subcutaneous (SAT) adipose tissue <sup>[172]</sup>. It is believed to be a compensatory action. In agreement with this circulating Irisin amounts are escalated in NAFLD patients, besides being positively associated with portal inflammation <sup>[173]</sup>, that is further thought to be a compensatory action.

## Visfatin

Visfatin represents an inflammatory adipokine enzyme (alias nicotinamide phospho ribosyl transferase as well as pre B cell colony enhancing factor). Visfatin amounts are escalated in T2DM in addition to insulin resistant situations <sup>[174]</sup>. Circulating Visfatin amounts are further escalated in NAFLD patients, besides being correlated with hepatic steatosis as well as fibrosis <sup>[175]</sup>. Nevertheless, they don't get influenced by insulin sensitizers like pioglitazone, rosiglitazone as well as metformin <sup>[176]</sup>.

### 4.4 NAFLD as well as - NASH --Obtained HCC

#### Pathogenesis of NAFLD as well as - NASH -- associated -HCC

HCC being the 3rd commonest etiology of cancer associated mortality <sup>[177]</sup>. NAFLD as well as NASH associated HCC represents the most rapidly escalated indication for liver transplantation <sup>[178]</sup>. Cirrhosis exists in about 60% of cases of NAFLD as well as NASH associated HCC <sup>[178]</sup>. This points that HCC can get stimulated from NAFLD as well as NASH without cirrhosis. Hence belief is that inflammatory parameters will also have a key part in NAFLD/NASH-obtained HCC.

#### Gut obtained endotoxin

Already detailed how Gut obtained endotoxins work in the form of alternative inflammatory parameters have a significant part in the generation of NAFLD/NASH. The amounts of LPS, alias endotoxins are further escalated in portal as well as peripheral venous veins of patients with HCC <sup>[179]</sup>. They facilitate significantly the invasion potential besides inducing epithelial –mesenchymal transition

(EMT), despite them hampering tumor growth as well <sup>[180]</sup>. LPS stimulates JNK in addition to MAPK through TLR4 in HCC cells while hampering of JNK in addition to MAPK causes a significant reduction in EMT taking place <sup>[180]</sup>. Hence the LPS-TLR4 signaling might be one of the lucrative pathways in controlling the propagation from NAFLD-NASH to HCC <sup>[181]</sup>.

## Adipokines

Adipokines represent inflammatory parameters associated with HCC generation. Expression of adiponectin in human HCC has an inverse association with the tumor size <sup>[182]</sup>. It escalates phosphorylation of c-jun N terminal kinase (JNK) as well as activation of caspase 3 resulting in apoptosis in HCC <sup>[182]</sup>. Hampering of JNK phosphorylation avoids anti apoptotic actions of adiponectin <sup>[182]</sup>. Adiponectin has a chemoshielding, besides hepatoshielding actions through sulfatase2 (SULF2) in HCC <sup>[183]</sup>. Adiponectin deletion facilitates fibrosis as well as HCC propagation in a choline deficient NASH mouse model <sup>[184]</sup>. Conversely high amounts of circulating adiponectin makes it feasible to anticipate the subsequent generation of HCC along with poor HCC survival <sup>[185]</sup>. Moreover adiponectin hampers the oncogenic action of leptin on cell proliferation, migration as well as invasion of HCC <sup>[155]</sup>.

Leptin expression is escalated in hepatoma tissues as well as cell lines <sup>[186]</sup>. Regulatory T Cells (TRegs), effector CD 4+T cells, as well as CD 8+T cells result in stimulation of the expression of the Leptin receptor (LEPR) in the liver following generation of HCC <sup>[186]</sup>. Macrophages as well as, dendritic cells, upregulate LEPR expression on the T Cells. Leptin hampers activation of TRegs as well as function <sup>[186]</sup>. Escalated Leptin expression in HCC is correlated with the expression of human telomerase reverse transcriptase (hTERT) <sup>[187]</sup>. Leptin might possess a key part in obesity associated tumorigenesis. Adipokines that include adiponectin along with Leptin are critical actors in obesity associated conditions as well as might be implicated in the etiopathogenesis of NAFLD as well as HCC.

Diagnostic as well as - Therapeutic target in NAFLD as well as - NASH --Obtained HCC-Hepatokines

The liver is an organ which liberates cytokines, known as hepatokines. Adipose tissue (AT) in NAFLD, having the properties of hepatic TG collection, has a key part in facilitation of FFA uptake into the liver via lipolysis <sup>[45]</sup>. Hence the part of adipokines from AT, that yields energy source for the generation of NAFLD, would be very significant in the liver. Conversely, lipid droplets collection by itself does not influence inflammation as well as is believed to be simple steatosis. The propagation from NAFLD to NASH to HCC needs extra factors

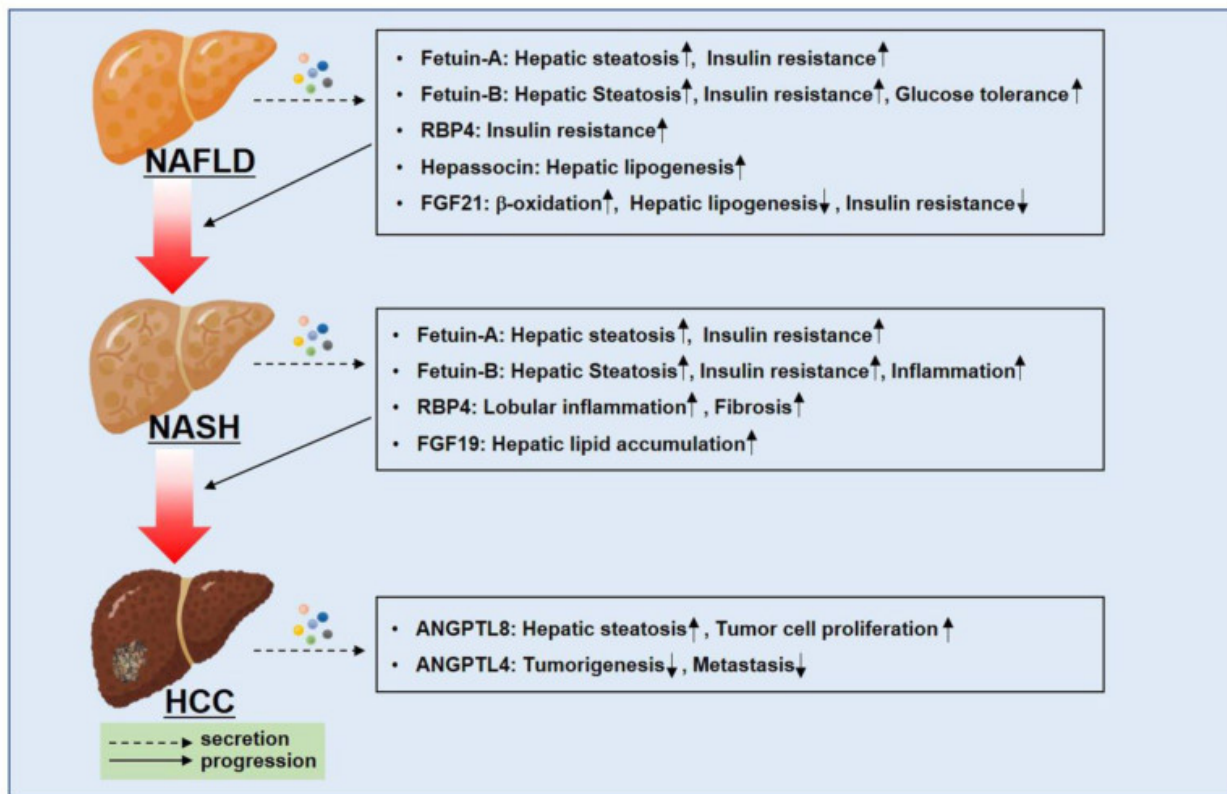


like oxidative stress, mitochondrial impairment as well as endoplasmic reticulum (ER) Stress [63,188]. Another significant factors facilitating NASH in simple steatosis is free nonesterified cholesterol as well as its oxidized products [189]. They are cytotoxic, influencing synergistic actions with TNF, that is markedly escalated in NASH patients [189]. Hence hepatokines liberated from liver might have an impact of potency in the propagation of NAFLD to NASH to HCC (Figure 6) greater propagation.

**α2-HS- glycoprotein (Fetuin A as well as - Fetuin B)**

Fetuin A, that is one of the liberated glycoproteins is believed to be the 1<sup>st</sup> hepatokine demonstrated to be correlated with metabolic diseases [190]. Fetuin A gets positively correlated with hepatic steatosis as well as IR1 [191]. Its amounts are escalated in patients with NAFLD, NASH in addition to T2DM [192]. In the form of a significant source of NAFLD generation, FFA escalates proinflammatory Fetuin A expression [24]. FFA stimulated Fetuin A works as an endogenous ligand of TLR4, as well as accelerates

lipid modulated insulin resistance [193]. FFA can further escalate the recruiting of NFκB to the Fetuin A promoter as well as escalate the generation as well as liberation of Fetuin A in primary hepatocytes [194]. Pioglitazone significantly represses serum Fetuin A amounts in patients with T2DM [195]. Pioglitazone hampers mRNA as well as protein amounts of hepatic Fetuin A along with oral delivery of pioglitazone in mice partly mitigated IR with reduction in hepatic Fetuin A expression [196]. These data point that Fetuin A might serve as a therapeutic target of NAFLD/ NASH as well as IR. Moreover circulating Fetuin A amounts are escalated in patients with HCC [197]. Fetuin B -might also work out to be an independent pointer of NAFLD generation [198]. It also stimulates hepatic steatosis, IR, glucose intolerance [166,199]. It results in phosphorylation amounts as well as exacerbates LXR/SREBP1c modulated hepatic lipogenesis [200]. Conversely, circulating Fetuin A as well as circulating Fetuin B amounts in NAFLD patients have a negative correlation with liver fibrosis [201].



**Figure 6.** the propagation of NAFLD to NASH to HCC

Legend for Figure 6

Courtesy ref no-30-Hepatokines that are secreted from the liver are closely associated with the progression from NAFLD to NASH to HCC. Hepatokines including Fetuin-A, Fetuin-B, RBP4, and FGF19 play an important role in NAFLD and NASH. They are associated with hepatic lipid accumulation, insulin resistance, and inflammatory signaling pathways. Additionally, ANGPTL4 and 8 tend to function in opposite ways in HCC tumorigenesis.

## Retinol Binding protein-4 (RBP4)

The liver has a central part in Vitamin A metabolism. In NAFLD hepatic Vitamin A homeostasis gets disturbed<sup>[202]</sup>. RBP4 is a particular Retinol/Vitamin A carrier protein liberated from the liver. Further it also gets liberated from adipocytes along with macrophages<sup>[203]</sup>. Serum RBP4 amounts are correlated with NAFLD generation<sup>[204]</sup>. Circulating RBP4 amounts have a positive association with body mass index (BMI) as well as IR<sup>[205]</sup>. In case of moderate to severe NASH, escalated amounts of RBP4 was association with lobular inflammation in addition to fibrosis scores<sup>[206]</sup>. In case of cirrhosis, expression of RBP4 escalated hepatic glucose generation, but not insulin sensitivity<sup>[207]</sup>. One knows that Vitamin A homeostasis is impaired in addition to decreased secondary to liver fibrosis as well as cirrhosis. Significantly escalated amounts of RBP4 might become a marker for NAFLD generation, along with the lower amounts of RBP4 might further be a marker for propagation of NASH with fibrosis in NAFLD stages<sup>[204]</sup>.

## Hepassocin (HPS)

Hepassocin is a hepatocyte obtained fibrinogen correlated peptide (HFREP-1), a hepatokine which is implicated in during liver regeneration<sup>[208]</sup>. In case of mice along with human patients with NAFLD, plasma HPS amounts are escalated<sup>[209]</sup>. Overexpression of hepessocin escalated hepatic lipid collection, besides NAFLD activity scores (NAS), while its removal enhances them<sup>[209,210]</sup>. Serum HPS amounts are escalated with the amounts of inflammatory cytokines in addition to lipogenic gene expression<sup>[210]</sup>. HPS stimulated hepatic steatosis gets triggered via the extracellular signal regulated kinase (ERK1/2)-based pathway<sup>[210]</sup>. FFA stimulates expression of HPS<sup>[211,212]</sup>. Oleic acid the maximum distributed unsaturated fatty acids, stimulates expression of HPS via the Signal Transducers and Activators of Transcription3 (STAT3) signaling<sup>[211]</sup>. Palmitate, that has the maximum content of saturated fatty acids, stimulates expression of HPS via endoplasmic reticulum (ER) stress – modulated p38 activation by C/EBP $\beta$  in primary hepatocytes<sup>[212]</sup>. In addition to that hepatic expression of HPS gets escalated by partial hepatectomy in mice, as well as gets stimulated by hepatic nuclear factor 1(HNF-1 $\alpha$ ) via the IL-6/STAT3 pathway<sup>[213]</sup>. Delivery of HPS confers protection against liver damage as well as escalates survival in rats with hepatitis<sup>[214]</sup>. Liver particular expression of HPS gets suppressed with the downregulation of the correlation of HNF1 alpha with reduced amounts of hepessocin in human Hepatocellular carcinoma<sup>[213,215]</sup>.

## Fibroblast -growth -factor 19 and -21 (FGF19 as well as - - FGF21)

FGF19 as well as FGF21 belong to the FGF19 family, which needs the Klotho proteins as cofactors. They stimulate FGFR4 along with Klotho, that has an abundance of expression in hepatocytes<sup>[216]</sup>. FGF19 as well as FGF21 have the role of controlling glucose, lipid as well as bile acid metabolism<sup>[217]</sup>.

## Fibroblast -growth -factor 19 (FGF19)

In case of NASH, the amounts of serum FGF19, Fibroblast growth factor receptor 4(FGF R4), along with bile acids are significantly escalated, that causes dysfunction of FXR as well as FGFR4 modulated signaling<sup>[218]</sup>. In cases of NASH, FAF analogue significantly causes reduction in hepatic lipid accumulation. Conversely up regulation of FGF19 is correlated with the propagation, recurrence, in addition to worst prognosis of HCC<sup>[219]</sup>. The  $\beta$ - Klotho proteins are further escalated in liver as well as serum of subjects with HCC<sup>[220]</sup>.

## Fibroblast -growth -factor 21 (FGF21)

The hepatokine FGF21 possess advantageous actions on hepatic lipid metabolism. It escalates lipid oxidation, represses DNL, in addition to escalate insulin resistance by inhibiting mammalian target of rapamycin complex 1 (mTOR)<sup>[221]</sup>. Hepatic FGF21 expression possesses a positive association with adipocyte in addition to intra hepatic TG, with its serum amounts being escalated by significant amounts in subjects with obesity, NAFLD as well as T2DM<sup>[222]</sup>. Serum amounts of FGF21 are escalated in obese children with or without NAFLD<sup>[223]</sup>. Escalated amounts of FGF21 are believed to be based on the robustness of steatosis, along with positive association with NAS<sup>[224]</sup>. Cases of advanced NASH can be labelled on the basis of properties of circulating FGF21 amounts in combination with inflammatory factors (cytokeratin 18, M30antigen, IL-1Ra, pigment epithelium-based factor, as well as osteoprotegrin)<sup>[225]</sup>. Enhancement of serum as well as hepatic FGF21 amounts are seen in cirrhosis as well as HCC<sup>[226]</sup>.

## Angiopoietin –Like Protein- 8 (betatrophin/ ANGPTL8)

ANGPTL8/betatrophin represent a circulating hepatokine also called TD26 as well as lipasin<sup>[227]</sup>. It is significantly expressed in liver as well as visceral adipose tissue (VAT)<sup>[228]</sup>. Over expression of ANGPTL8 in brown adipose tissue (BAT) escalates lipoprotein lipase (LPL)

action along with TG uptake <sup>[168,229]</sup> [reviewed by us in 169]. Serum ANGPTL8 are significantly escalated in patients with pre Diabetes as well as type2 Diabetes <sup>[230]</sup>. It has been documented that ANGPTL8 is not implicated in Pancreatic  $\beta$ cells expansion, although it has a part in controlling glucose along with lipid metabolism in mice <sup>[231,232]</sup>. In addition ANGPTL8 expansion is significantly escalated in HCC <sup>[228]</sup>. It crosstalks with SREBP1, secondary to which it facilitates lipogenesis along with tumor cell proliferation in HCC <sup>[228]</sup>. Hence it is believed that it has a positive association with the tumor size. ANGPTL8 needs ANGPTL 3 instead of controlling LPL by itself <sup>[229,233]</sup>. ANGPTL 3 controls TG metabolism by directly hampering LPL <sup>[229,233]</sup>. ANGPTL 4 gets markedly expressed in liver as well as adipose tissue, in addition to can controls TG metabolism by hampering LPL action <sup>[229,235]</sup>. Nevertheless, ANGPTL 4 expression reduction exists in HCC, besides Over expression of ANGPTL4 hamper hepatocarcinogenesis along with metastasis of HCC <sup>[236]</sup>.

## 5. Conclusions

Over the past 2 decades the percentage of HCC cases possessing non viral etiology has been escalating at a fast pace. Secondary to this the significance of NAFLD/NASH obtained HCC has been showing up. At present what holds the truth is that management of subjects with NAFLD/NASH is usually carried out with the utilization of medicines for the treatment of type2 Diabetes mellitus as well as hyperlipidemia. The adverse actions which show up following the long term utilization have to be taken into account. Hence proper therapeutic targets along with FDA approved treatments are required at war footing. It is believed that the causation of failure of generation of a therapy for subjects with NAFLD/NASH in spite of continuous attempts are i) pathogenesis is still not totally clear; ii) absence of actions; iii) safety issues. Adipose tissue as well as the liver constitute the most significant organs that are correlated with lipid metabolism. Hence it is essential to watch adipokines as well as hepatokines that can work as diagnostic in addition to therapeutic targets as well as signaling pathways that get targeted by the present therapies. In addition, to that it needs to get deep insight via the classification as per the etiology of NAFLD. It would yield a significant point of view for the regulation of the metabolic phenotype from NAFLD to NASH to HCC. At present it has been accepted that think of NAFLD as being occurring secondary to a concert of different parameters that include nutritional factors, Gut Microbiota, genetic in addition to epigenetic factors as well as adipokines in addition to hepatokines. To be able to achieve a successful therapy, it is essential to watch different factors in a wider

perspective.

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