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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 steatohepapititis (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; hepatosscin; retinol binding protein 4; treatment like pioglitazone; liraglutide; elafibranor CVC (cerviciroc); obeticholic acid; aramchol; selonosertib; 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 steatohepapititis (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-

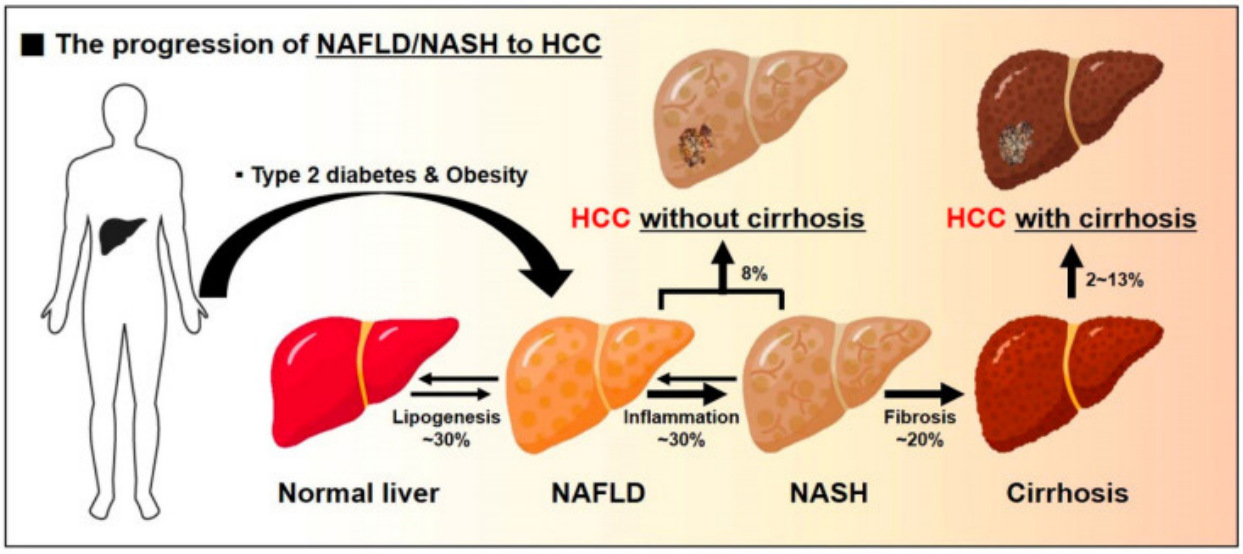


**Figure 1.** The progression of NAFLD/NASH to HCC

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.

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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 [43]. 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 adipoklines/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; Hepatokines; angiopoietin like protein 2; hepatosscin; retinol binding protein 4; treatment like pioglitazone; liraglutide; elafibranor CVC (cerviciroc); 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 Steatohepapititis (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 [26]. Hence the balance among FA input as well as -output is key [44]. 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 [45], 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 [FAT]) as well as, fatty acids binding protein (FABP) [46]. 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) [47]. DNL represents metabolic event which is implicated in generation of new FA from escalated glucose [48]. It significantly aids in hepatic lipid collection in etiopathogenesis of NAFLD [48]. 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 [49]. 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 [45].

The maximum lucrative theory in etiopathogenesis of NAFLDis "2hit" posit [50]. 1st hit is IR, secondary to escalated FA flux, $2^{ND}$ 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 [51]. 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 [52]. Normally, Endotoxin can get absorbed from the lumen of the intestine into theportal venous system in addition to absorbed endotoxin would get cleared fast by the reticulo endothelial system, specifically kupffer cells [53]. Never-



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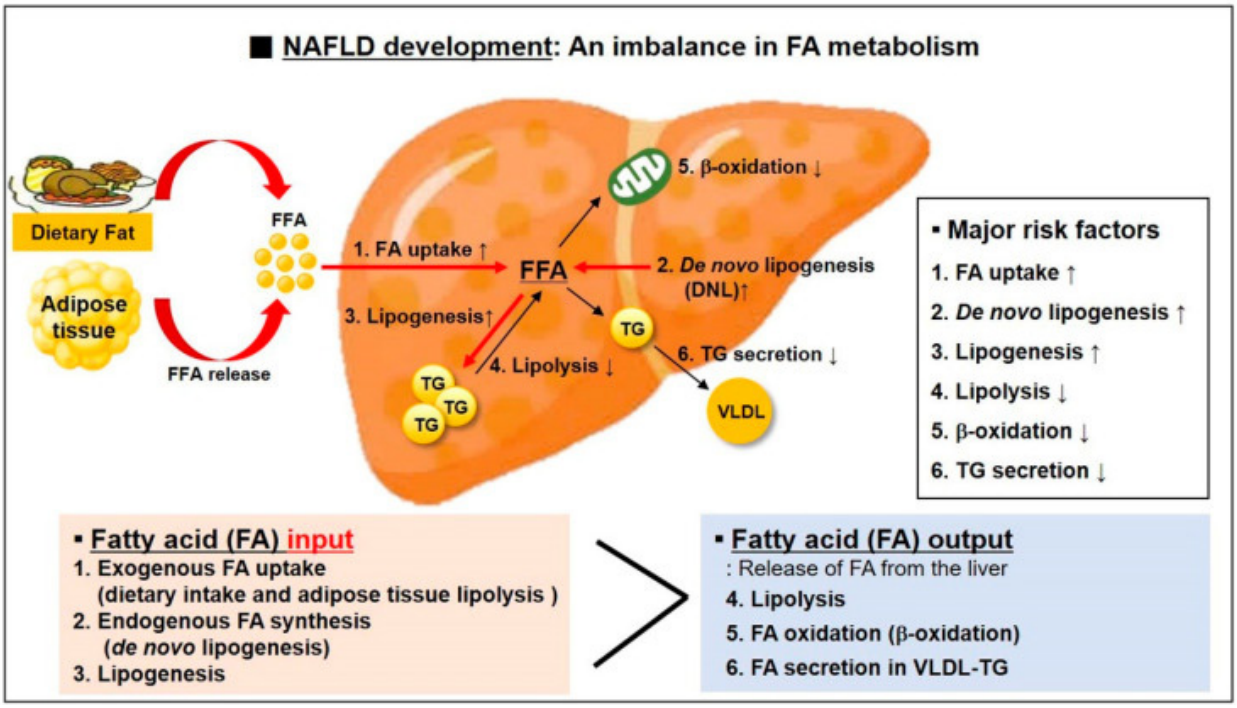


**Figure 2.** NAFLD development: An imbalance in FA metabolism

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 [54]. These invasive pathogenic deleterious by products have an impact on the liver lipid collection along with acceleration of proinflammatory in addition to fibrosis events [53].

The part of LPS from gut microbiota (GM) in the generation of NAFLD as well as NASH has been highlighted [54]. 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 [54,56]. 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 [57]. LPS results in acceleration of liver damage in mice receiving a diet lacking methionine-choline [58]. The LPS binding protein LBP-CD14 complex results in stimulation of TLR4, that is necessary cascade needed for inflammatory propagation [59]. Once LBP deletion occurs it ameliorates inflammation modulated liver damage [60]. 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 [61]. 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 [51,62]. In the form of -Pharmacological treatmentsin NAFLD as well as NASH which target the microbiome, IMM-24 (an anti-LPS antibody), solithromycin (next generation macrolide antibiotic) along with TLR4 antagonist [63].

## Oxidative stress

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

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process occurring generally in NAFLD as well as NASH secondary to escalated generation of Reactive oxygen species (ROS) [64]. ROS in addition to lipid per oxidation 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 κB (NFκB), which causes upregulation of TNFα [68]. Hence it further aids in dysfunctional mitochondrial respiration in addition to escalation of ROS generation [68].

Escalation of mitochondrial β-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 F2α (8-isoPGF2α) 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-isoP-GF2α 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 variablility 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 montherapy 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].



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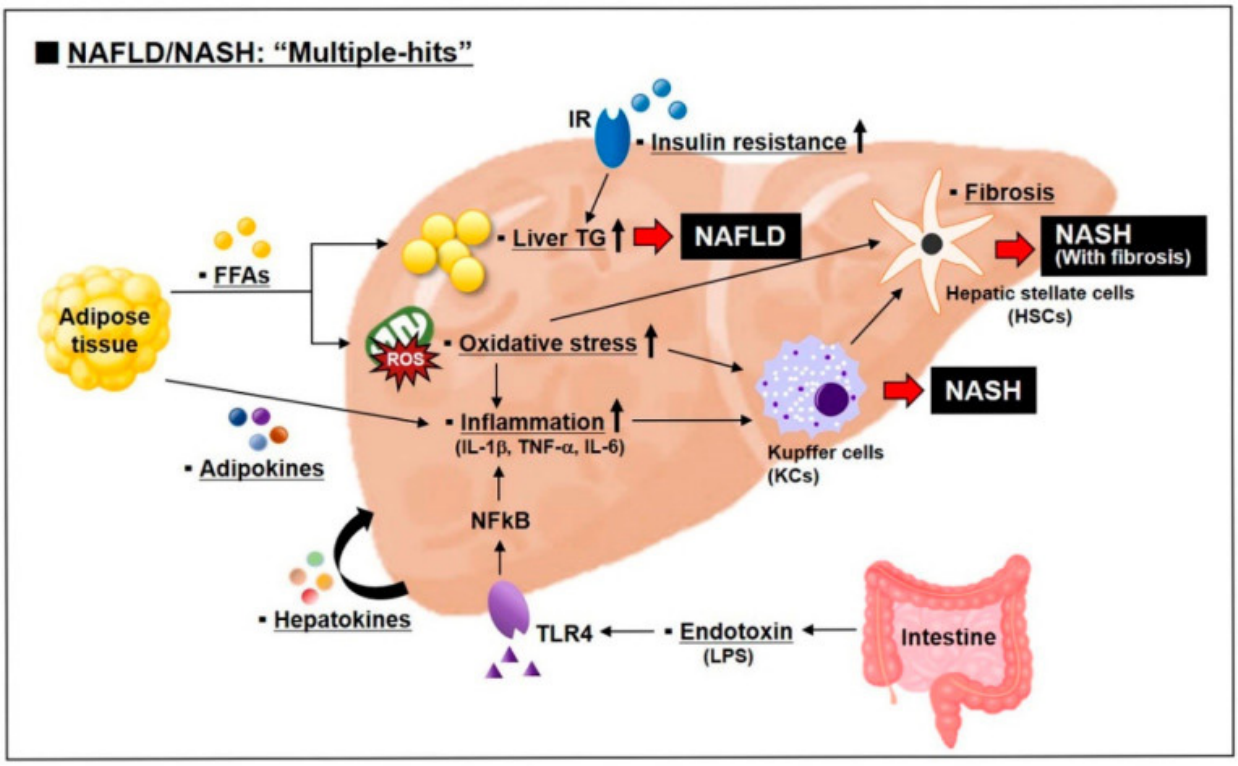


**Figure 3.** NAFLD/NASH: "Multiple-hits"

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).

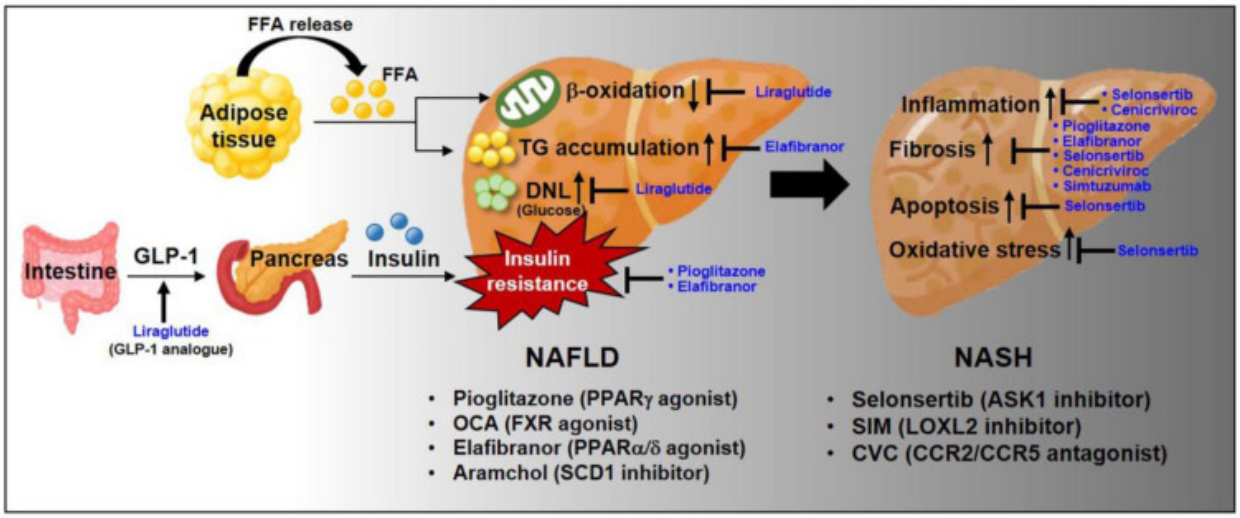


**Figure 4.** Pharmacological examples

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.

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TZD's work by controlling metabolic pathway by binding to the nuclear transcription factor Peroxisome Proliferator adenineActivated Receptor γ (PPAR γ) in addition to modulation of the expression of the target genes [86]. The genes possess a part in controlling glucose metabolism, storage of FA's along with adipocytes differentiation [87]. In agreement with this PPAR γ agonist escalated the expression of glucose transporter 4 (GLUT4alias SLC2A4) A as well as translocation, hamper TNFα as well as result in enhancement of insulin sensitivity in case of organs which are insulin sensitive [88]. Conversely T2D treatment effects increments of weight as an adverse action, since PPAR γ Receptor's are markedly expressed in adipocytes [89]. Enhancement of fat mass is restricted to the subcutaneous adipose depots instead of the visceral area [88,90]. That can be prevented by metformin therapy [91].

Recently it got documented that the PPAR γ agonist Pioglitazone possesses significant actions on NAFLD/NASH patients. In case of patients with NASH, it amelioratedliver fat collection along with fibrosis [92]. 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 [93]. In rodent models it decreases hepatic gluconeogenesis along with results in escalation of insulin sensitivity in the liver as well as other peripheral tissues [94].

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

Obeticholic acid (OCA) represents a Farsenoid 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 [95]. In rodent models OCA has anti-inflammatory along with, anti-fibrotic actions on HSC's as well as macrophages [96]. The transcriptional repressor small or short heterodimer partner (SHP), crossreacts with liver receptorhomolog1 (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 [97]. HSC's getting exposed to FXR ligands escalated the expression of the transcriptional repressor SHP along with reduction of factors correlated with liver fibrosis [96]. 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 chenodeoxycholic acid, that is a natural FXR agonist [98]. 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 [99].Weight reduction results in patients with NASH, with this weight reduction having extra advantageous actions on SerumALT/ASTamounts along with liver histology [100]. In addition to that it results in significant enhances fibrosis in patients with NASH [101]. It represents 1 of the agents holding maximum promise for NASH therapy, is in phase 3 trials [102].

## 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 [103]. Their expression occurs in liver, adipose tissue (AT), heart, skeletal muscle, as well as kidney, besides controlling -β -oxidation along with gluconeogenesis [102]. Three kinds of nuclear receptor isoforms exist; PPARα, PPAR δ, as well as PPARγ. PPARα, facilitates β -oxidation, decreases triglycerides (TG), amounts, besides escalated high density lipoprotein (HDL) cholesterol amounts [104]. Further it hampers nuclear factor κB (NFκB) stimulation of inflammatory genes [104]. PPARα 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 [105]. The reason for this is the existence of PPARα in a lot of organs besides liver. Akin to PPARα, PPAR δ causes escalation of FA oxidation along with decreases macrophages in addition to Kupffer cells activation, in view of its existence on macrophages [106]. GW50516 represents a synthetic PPAR δ particular agonist [107]. GW50516 can be thought of as attractive proposition in Clinical trials, in view of it possessing potent efficiency, however it possesses safety issues [108].

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



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

## 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 β -oxidation [117]. Furthermore it results in stimulation of cholesterol efflux by activation of the ATP – binding cassette transporterA1 (ABCA1) [118]. Additionally, it decreases inflammation as well as fibrosis in methionine as well as choline deficient (MCD) fed mice [116]. Moreover it tends to ameliorate steatohepapititis 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 [116].

In a phase 2 trial, of patients with NAFLD, Aramchol decreased the liver fat amounts along with liver histology [119]. No significant toxicity was observed as seen in circulating ALT as well as AST amounts, besides alkaline phosphatase (AP) amounts [119]. 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-1Agonist)

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 [120]. GLP-1 represents an incretin hormone liberated from the L-cells in the distal ileum along with colon [121]. It causes stimulation of pancreas resulting in insulin generation, in addition to decreases glucagon generation [122]. Endogenous GLP-1 gets broken down by Dipeptidyl Peptidase-4 (DPP-4) enzyme within few minutes whereas Liraglutide possesses long half life 13h [123].

Exenatide that is a synthetic Extendin-4 was the 1st 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 [124].

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 [125]. It possesses cardiovascular safety while treatment for weight reduction [126]. Anorexia secondary to Liraglutide is associated with glutamatergic POMC neurons, resulting in weight reduction [127]. 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 deterioratrion of fibrosis [[128]. In view of rodent studies demonstrating Liraglutide conferred protection to pancreatic β cells from apoptosis via AKT modulated survival signaling [129]. It enhanced insulin sensitivity by activation of adenine monophosphate activated -protein kinase (AMPK) as well as decreases hepatic steatosis by modulation of lipid transportation, β-oxidation, DNL, as well as autophagy [130].

## Selonsertib (ASK1 Inhibitor)

Balooning of hepatocytes, points towards the stimulation of the apoptosis pathway, which represents a hallmark of NASH along with fibrosis propagation [131]. Selonsertib represents -1ST in class Inhibitor of the apoptosis signal regulating kinase 1 (ASK1) [132]. 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 ofc-Jun –N terminal kinase (JNK) resulting in activation of stress response pathways which exacerbate hepatic inflammation, apoptosis in addition to fibrosis [133]. 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 [133]. 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 [134]. 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 [135].

## Simutuzumab (SIM;G6624)

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

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trix (ECM) [136]. SIM binds TO LOXL2 as well as hampers its enzymatic action [137]. Hence it hampers the generation of growth factors that includes [connective tissue growth factor (CTGF]/CCN2) as well as TGFβ1 in addition to results in reduction of fibrosis [138]. In a mouse model possessing advanced fibrosis stimulated by NASH, SIM possesses an extra action in combination with the ASK1 Inhibitor [134]. 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 [139].

### 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 [140]. 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 [140,141]. CCR2 in addition to its ligand CCL2 escalated hepatic steatosis, macrophages collection, inflammation along with fibrosis [140]. 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 [141].

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 [142]. CVC results in reduction of markers of inflammation like IL-1β, IL-6 as well as influences antifibrotic actions [142]. 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 [143]. At present a phase 3 clinicaltrial is ongoing for the therapy of NASH cases with liver fibrosis [144].

### 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 [78]. Of these we concentrate on adipokines liberated from adipose tissue (AT) which yield fatty acids (FA) as the main site aiding for NAFLD generation [45]. Various Adipokines are implicated in the pathogenesis as well as propagation of NAFLD [145]. Leptin, resistin, in addition to visfatin have a part in NAFLD generation as well as propagation of NASH [145,147]. Conversely adiponectin, irisin as well as ghrelin have advantageous actions on NAFLD as well as NASH [148,149]. 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 [150]. They had an inverse association with the robustness of hepatic steatosis as well as inflammation. Pioglitazone, the antidiabetc which had a beneficial action on liver histology escalated adiponectin amounts, in patients withNASH [93]. Nevertheless, metformin the commonest used antidiabetc agent did not have any significant actions on either the liver histology but decreased the adiponectin amounts [89,151]. Vitamin E has a robust antioxidant action that can confer protection to bodies cells against Oxidative stress [152]. 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 [153]. Nevertheless, it has no efficacy in NASH cases with T2DM [153]. In case of mouse models, adiponectin represses hepatic lipid collection by lipid metabolism collection by escalated FA oxidation along with reduction in DNL [94]. Adiponectin has anti inflammation, anti fibrotic as well as anti apoptosis action [154]. Adiponectin delivery escalates hepatic steatosis along with inflammation [154]. Moreover adiponectin expression has an inverse association with tumor size as well as recurrence [155].

### 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 [156]. In animal models it is believed to escalate lipid metabolism in case of non AT's [157]. Nevertheless, in liver, it accelerates hepatic IR, that results in liver steatosis. Further it escalates -liver fibrosis [156]. Leptin delivery might



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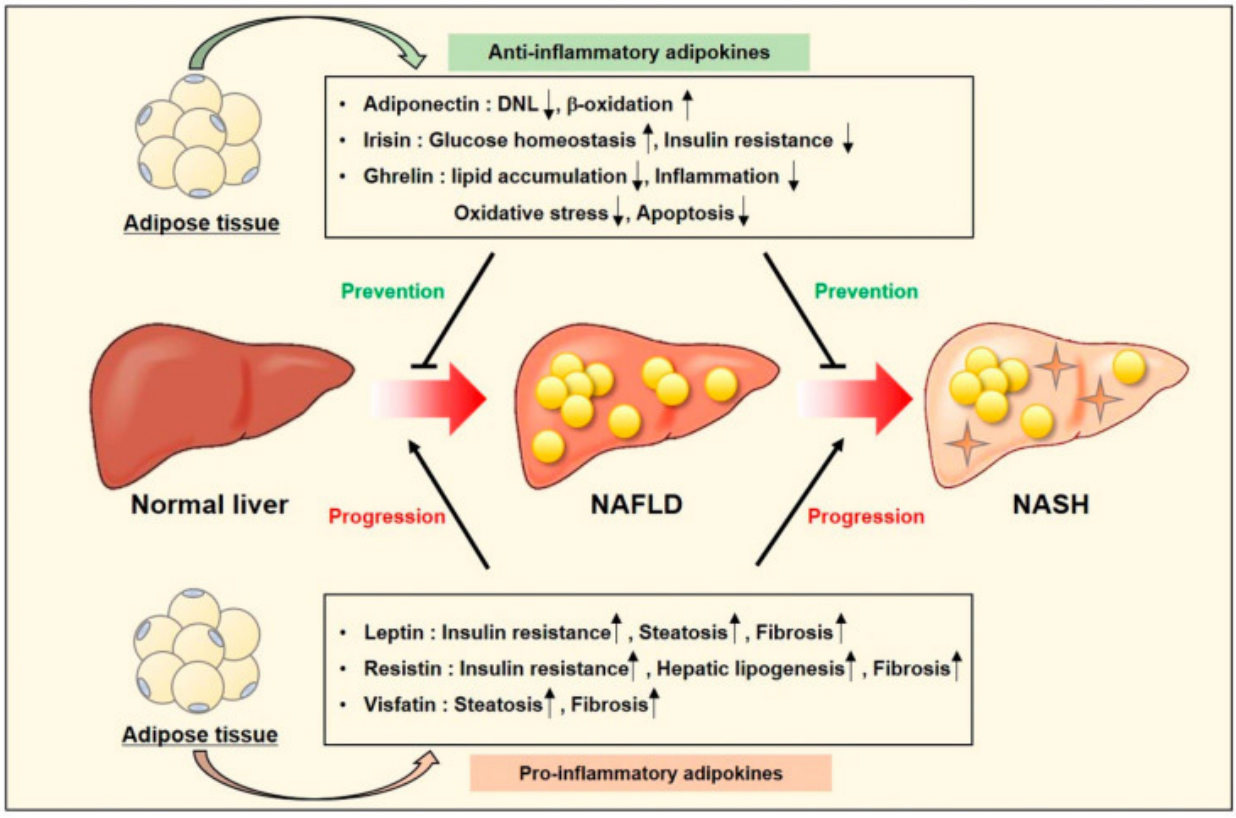


**Figure 5.** NAFLD robustness anticipation

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) [158]. Nevertheless, in humans its actions are not certain. Escalated circulating amounts are present in patients with NASH [159]. Leptin expression has a positive association with robustness of steatosis, inflammation along with fibrosis [160]. Leptin expression has a positive association with cell proliferation in HCC, as validated by proliferation marker Ki67 [133].

## Resistin

Resistin is a proinflammatory adipocyte obtained modulator of hepatic IR [161]. Further it gets expressed in liver as well. It is correlated with hepatic lipogenesis as well as liver fibrosis [162]. 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 [162]. 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 [163].

## 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 [164]. In patients with NAFLD lesser Ghrelin are correlated with IR [165]. 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 [43]. At the time of as well as following NAFLD generation, Ghrelin delivery escalates lipid metabolism, inflammation, Oxidative stress as well as apoptosis [166]. 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 [167]. In toto Ghrelin might work as a biomarker for both diagnosis and management of non alcoholic fatty liver disease.

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### Irisin

Irisin is a myokine liberated from skeletal muscles on shivering in addition to exercise stmn [168,169]. Fibronectin typeIII domain containing 5 precursors (FNDC5) is the precursor of Irisin. FNDC5/Irisin facilitate thermogenesis in AT via ERK as well as p38pathways [170]. It causes enhancement of glucosehomeostasis along with IR, besides resulting in weight [171] 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 [172]. 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 [173], 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 [174]. Circulating Visfatin amounts are further escalated in NAFLD patients, besides being correlated with hepatic steatosis as well as fibrosis [175]. Nevertheless, they don't get influenced by insulin sensitizers like pioglitazone, rosiglitazone as well as metformin [176].

### 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 [177]. NAFLD as well as NASH associated HCC represents the most rapidly escalated indication for liver transplantation [178]. Cirrhosis exists in about 60% of cases of NAFLD as well as NASH associated HCC [178]. 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 [179]. They facilitate significantly the invasion potential besides inducing epithelial –mesenchymal transition (EMT), despite them hampering tumor growth as well [180]. 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 [180]. Hence the LPS-TLR4 signaling might be one of the lucrative pathways in controlling the propagation from NAFLD-NASH to HCC [181].

### Adipokines

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

Leptin expression is escalated in hepatoma tissues as well as cell lines [186]. 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 [186]. Macrophages as well as, dendritic cells, upregulate LEPR expression on the T Cells. Leptin hampers activation of TRegs as well as function [186]. Escalated Leptin expression in HCC is correlated with the expression of human telomerase reverse transcriptase (hTERT) [187]. 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 [45]. 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



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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 1st 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 Ain 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].

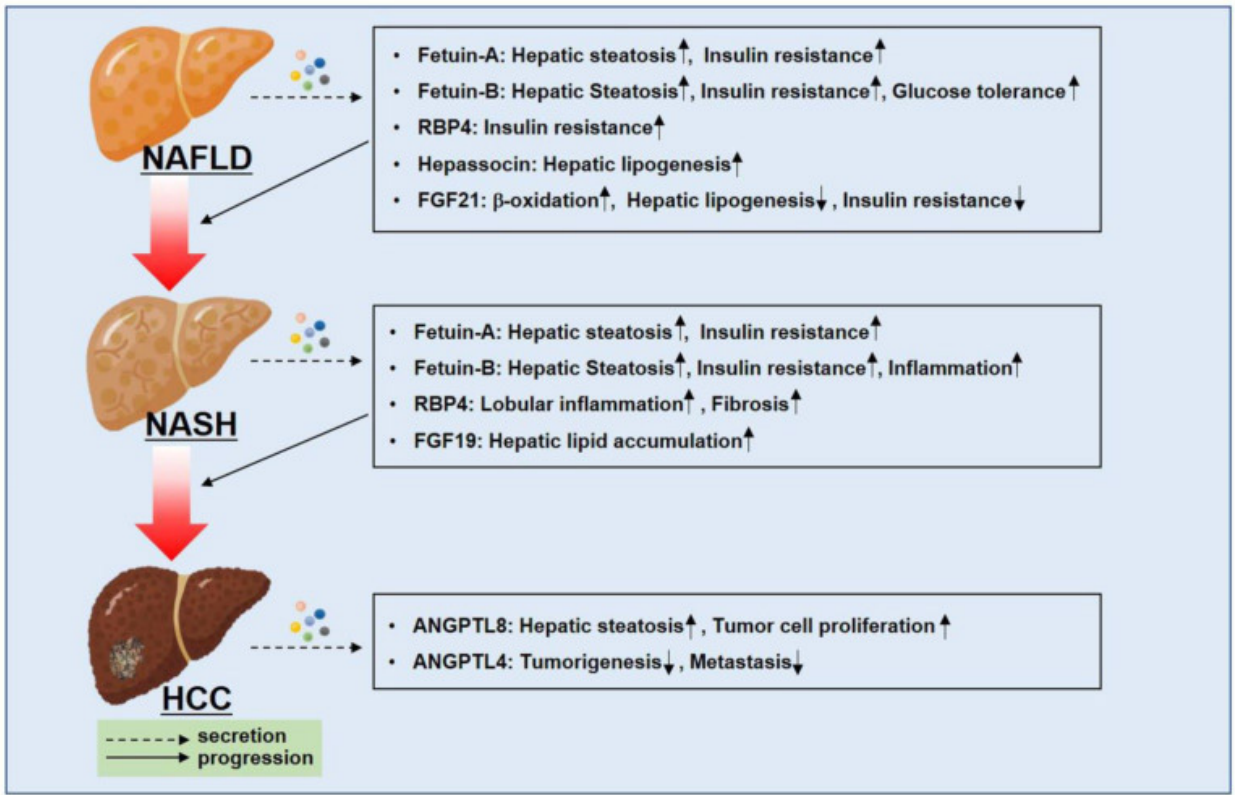


**Figure 6.** the propagation of NAFLD to NASH to HCC

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.

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### Retinol Binding protein-4 (RBP4)

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

### Hepassocin (HPS)

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

### 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 [216]. FGF19 as well as FGF21 have the role of controlling glucose, lipid as well as bile acid metabolism [217].

### 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 [218]. 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 [219]. The β- Klotho proteins are further escalated in liver as well as serum of subjects with HCC [220].

### 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 complex1 (mTOR) [221]. 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 [222]. Serum amounts of FGF21 are escalated in obese children with or without NAFLD [223]. Escalated amounts of FGF21 are believed to be based on the robustness of steatosis, along with positive association with NAS [224]. 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) [225]. Enhancement of serum as well as hepatic FGF21 amounts are seen in cirrhosis as well as HCC [226].

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

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



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

## 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.

## References

[1] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Kochar Kaur -K,Allahabadia GN,Singh M(2016). An update on Aetiopathogenesis and management of Obesity.Obes Control Ther3(1):1-17. Diabetes Res Clin Pract 2014;103:137-49.

[2] Kochar Kaur -K,Allahabadia GN,Singh M(2013) Current management of obesity in an infertile female. Recent Advances -and Future Prospectives.Drugs J Pharm Nutr Soc;3:1-13.

[3] Kochar Kaur -K,Allahabadia GN,Singh M .Therapeutic Utilization of Neuro Imaging Studies in Obesity for Optimal Utilization of Drugs used in Treatment for Obesity-Lessons Learnt from Bariatric Surgery. -J Ageing Restor Med (JARM)n2019;2(2):89-97.

[4] Kochar Kaur -K,Allahabadia GN,Singh M . Existing and prospective pathways for intervention in treatment of obesity in a novel way-a review; -*MOJ Drug Des Develop Ther.* 2018;2(3):95-105. DOI: 10.15406/mojddt.2018.02.00035.

[5] Kochar Kaur -K,Allahabadia GN,Singh M .Advances in BAT physiology for understanding and translating into Pharmacotherapies for obesity and comorbidities. *MOJ Drug Des Develop Ther.* 2018;2(5:166-176.

DOI: 10.15406/mojddt.2018.02.00057.

[6] Kochar Kaur -K,Allahabadia GN,Singh M. Targeting macrophage polarization for therapy of diabesity–the feasibility of early improvement of insulin sensitivity and insulin resistance-a comprehensive systematic review. J Diab Metab Disorder Control. 2021;8(1):6-25.

[7] Kochar Kaur -K,Allahabadia GN,Singh M. Are we at the verge of finding a new efficacious pharmacotherapy for obesity in the form of agonism at triple drug receptors: glucagon, Glucagon like peptide1 (GLP1), glucose dependent insulin tropic peptide (GIP). *MOJ Drug Des Develop Ther.* 2019;3(1):22-27.

[8] Kochar Kaur -K,Allahabadia GN,Singh M. Targeting Orexin Neurons for Treatment of Obesity is It Feasible in Human Being-A Systematic Review. Journal of Neurology Research Reviews & Reports. J Neurol Res Rev Rep, 2019; 1(1): 1-9.

[9] Kochar Kaur -K,Allahabadia GN,Singh M .Importance of simultaneous treatment of obesity and diabetes mellitus: A sequelae to the understanding of diabesity-A review.*Obes Res Open J*. 2019; 6(1): 1-10. DOI: 10.17140/OROJ-6-136.

[10] Kochar Kaur -K,Allahabadia GN,Singh M . Role of

Adipocyte Impairment in Heart Failure Induction in Subjects that are Obese along with Prediabetes and Overt Diabetes Mellitus - A Systematic Review. International Journal of Cardiology and Cardiovascular Disorder2021; 2(1) :1-21.

[11] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. A Mini Review on Development of Newer Therapies for Non Alcoholic Fatty Acid Liver Disease with Emphasis on Vitamin D and its Receptor and Allyl Isothiocyanate (AITC)". Acta Scientific Nutritional Health 2019; 3(12) :1-5.

[12] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. An Update on Further Progression of NAFLD, NASH with Prospective Therapies Like L-Carnitine (LC), Nicotinamide Ribose (NR) Combination, as well as Apical Sodium Dependent Bile Acids Transporter (ASBT) or Volixibat and Silybin as Alternatives. Int J Clin Med Cases. 2020 Jan;3(3):138.
DOI: 10.31021/ijcmc.20203138-29/1/2020 jan 29.

[13] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Have Probiotics and Synbiotics passed the test of time to be implemented in management of obesity and related metabolic disorders-a comprehensive review. *Adv Obes Weight Manag Control*. 2019;9(1):21-28.
DOI: 10.15406/aowmc.2019.09.00269.

[14] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Will Probiotics Provide the Answer for Therapy of Non-alcoholic Fatty Liver Disease (NAFLD)? – A Systematic Review. Biochem Physiol -2020;9: 257.

[15] Kulvinder Kochar Kaur,Allahbadia GN,Singh M.. Rosmarinic Acid-A New Hope for Liver Diseases Like Cirrhosis, Hepatocellular Carcinoma-NeedsTranslation to Humans". EC Endocrinology and Metabolic Research 2019;4(6 ): 289-301.

[16] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. How do we apply advances in knowledge of Hepatic Macrophages in treating Liver Diseases especially non alcoholic -fatty liver disease( NAFLD), non alcoholic steatohepapititis( NASH), with the increasing incidence of Diabesity-A Systematic Review.EC Endocrinology and Metabolic Research published in2020.

[17] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Mechanisms that associate extension of Nonalcoholic fatty liver diseases(NAFLD) to NASH (Nonalcoholic steatohepatitis) and further progressing to cirrhosis and Hepatocellular carcinoma(HCC) in addition to few proposed biomarkers for poor prognosis.J Gynaecol 2021;1(16):1-18.

[18] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. How can we optimize therapy of Non Alcoholic Fatty Acid Liver Disease-A Short Communication on role of Astragaloside IV and other prospective agents". Clinical Research and Clinical Case Reports, 2021;1(3):1-4;
DOI: http;//doi.org/04.2021/1.1013.

[19] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Paradoxical Additional Role of SGLT2 Inhibitors Beyond Glycosuria in Controlling Obesity, NAFLD Treatment, Pancreatic β Cell Protection Besides Therapy for Diabetes Mellitus, CVOT and Renoprotection-A Minireview". *Acta Scientific Gastrointestinal Disorders* 4.7 (2021): 15-26.

[20] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. 'An update on management of Nonalcoholic Fatty Liver Disease &Nonalcoholic Steatohepapititis-Is -the time ripe for achieving -resolution of NAFLD &NASH soon''.2021Under review.

[21] Khan MAB,Hashim MJ,King JK,Govender RD,Mustafa H,AlKaabi J. -Epidemiology of type2 Diabetes mellitus- Global burden of disease and forecasted trends.J Epidemiol Glob Health 2020;10:107-11.

[22] Masmiquel L,Leiter LA,Vidal J,Bain S,Petrie J,-Franek E,etal.LEADER 5: Prevalenceand cardiometabolic impact ofobesity in cardiovascular high risk patients with type2 Diabetes mellitus:baseline global date from the LEADER trial. Cardiovasc Diabetol 2016;10:29.

[23] Ng ACT,Delgado V,Borlaug BA,Bax JJ.Diabesity :the combined burden of obesity -and Diabetes on heart disease and the role of imaging .Nat Rev Cardiol 2021;108:291-304.

[24] Gonzalez-Gross M,Melendez A.Sedentarism,active lifestyle and sport:impact on health and -obesity prevention.Nutr Hosp2013;5:89-98.

[25] Younossi ZM .Nonalcoholic fatty liver disease a global public healthperspective. J Hepatol 2019.;70: 531-44.

[26] Sunny NE,Bril F,Cusi K. Mitochondrial Adaptation in non alcoholic -fatty liver disease:novel mechanisms and treatmentstrategies. Trends -Endocrinol Metab 2017; 28:250-60.

[27] Abd-El-Khader SM, El-Den Ashwamy EM. Nonalcoholic fatty -liver disease:the diagnosis and management. World JHepatol 2015; 7:846-58.

[28] Arulanadan A,Loomba R.Non invasing testing -for NASH and NASH with advanced fibrosis:are we there yet?Curr Hepatol Res 2015;14: 109-18.

[29] Chalasani N, Younossi ZM, Lavine AE,Charlton M, Cusi K, RinellaM, -etal .The diagnosis and management of - non alcoholic fatty liver disease: practice

  DOI: https://doi.org/10.30564/jer.v3i2.3520

guidance from the -American -Association for thestudy of - Liver disease. -Hepatology -2018;67: 328-57.

[30] Kim H, Lee DS,An TH,Park HJ,Kim WK,Bae KH,Oh KJ.Metabolic spectrum of liver failure in type2 - Diabetes and obesity:From NAFLD to NASH to HCC.Int J Mol Sci 2021;22:4295.

[31] Mahjoubin-TehranM,DeVentisA.Mikhailidis DP,Atkin SL,Mantzoros CS,Jamialahmadi T, -etal . Nonalcoholic fatty liver disease and steatohepatitis:state of the art on effective therapeutics based on the gold standard method for diagnosis. Mol Metab 2020;13:101049.

[32] Loomba R.Adams LA.The 20% rule of NASHprogression:the natural history of -advanced fibrosisand cirrhosis caused by NASH. Hepatology 2019;70: 1885-88.

[33] Wong SW,Ting YW,Chan WL. Epidemiology of -non alcoholic fatty liver disease related Hepatocellular carcinoma and its implications.JGH Open 2018;2: 235-41.

[34] BenhammouJN,Lin J,Hussain SK, El-Kabany M.Emerging risk factors for non alcoholic fatty liver disease - -associated Hepatocellular carcinoma. Hepatoma Res -2020;6:35.

[35] Huang DQ,El-SeragHB, Loomba R. Global Epidemiology of NAFLD- related HCC:Trends ,predictions,riskfactors and prevention. Nat Rev -Gastroenterol -Hepatol 2021;18:223-38.

[36] Anstee QM,McPherson S,Day CP.How big a problem -is Nonalcoholic fatty liver disease?BMJ2011;343:d3897.

[37] Tomah S,Alkhoury N,Hamdy O. Nonalcoholic fatty liver disease and type2 Diabetes:where do Diabetologists stand? Clin Diabetes Endocrinol 2020;6:9.

[38] Jarvis H,Craig D,Barker R,Spiers G,Stow D, Anstee QM, -etal .Metabolic risk factors -and incident advanced liver disease in Nonalcoholic fatty liver disease(NAFLD) :a systematic review and -meta-analysis of -population -based observational studies.PLoS Med 2020;17:e1003100.

[39] Miya narsky L,Manchem Y,Shibolet O. Treatment of Hepatocellular carcinoma:steps forward but but still a long way to go. World JHepatol 2015; 7:566-74.

[40] Goto K,Roca Suarez AA,Wrench F,Baumert TF,Lupberger J.Virus and Hepatocellular carcinoma:when the host loses its grip. Int J MolSci 2020;21):3057.

[41] Enomoto H,Ueno Y,Hiasa Y,Nishikawa H,Hige S,Taki kawa Y, -etal .Japan etiology of LiverCirrhosis Study Group in the 54th annual meeting of JSH.The transition in the -etiologies of -Hepatocellular carcinoma-complicated LiverCirrhosis in anationwide survey of Japan.J Gastroenterol -2021;56:158-67.

[42] Kinoda T, Goto K,Hirotsu Y,Masuzaki R,Moriyama M,Omata M. Molecular mechanisms :connections -between Nonalcoholic fatty liver disease, steatohepapititis and Hepatocellular carcinoma. Int J MolSci 2020;21):1525.

[43] Kim WK,Bae KH, Lee SC,Oh KJ.The latest insights into adipokines in -Diabetes. J Clin Med - - 2019; 8:1874.

[44] David Hojland L,Kykkesfeldt J,Tveden Nyborg . Molecular mechanisms of hepatic lipid accumulation in Nonalcoholic fatty liver disease. Cell Mol Life Sci -2018;75: 3313-327.

[45] Donnelly KL,Smith CI,Schwazenberg SJ,Jessurun J,Boldt MD,Parks EJ.Sources of fatty acids stored in liver and secreted via lipoprotein in patients with - non alcoholic fatty liver disease. J Clin Invest 2005;115:1343-51.

[46] Michele AB, David EC. Triglyceride metabolismin the liver .Compr Physiol -2017;8: 1-8.

[47] Draison F,Moulin P,Beylot M.Contribution of -hepatic Denovo lipogenesis and resterification of plasma non esterified fatty acids to plasma Triglyceride synthesis in Nonalcoholic fatty liver disease. Diabetes -Metab -2003;29:478-85.

[48] Chiu S,Mulligan K,Schwartz JM.Dietary arbohydrate and fatty liver disease: Denovo lipogenesis. Curr -Opin Clin Nutr Metab Care 2018;21:277-82.

[49] Linden AG,LiS,Choi HW,Fang F,Fukasawa U, Ueda K, -etal .Interplay between ChREBP and SREBP1c coordinates -postprandial glycolysis and lipogenesis -in livers of mice.J Lipid Res -2018;59: 475-87.

[50] Day CP,James OF. Steatohepapititis:A tale of two hits? Gastroenterology 1998;114:842-45.

[51] Arrese M,Cabrera D,Kalergis AM,Feldstein AE. Innate immunity and inflammation in NAFLD/ NASH. Dig Dis Sci 2016;61:1294-1303.

[52] Fukut H.Gut- liver axis in liver cirrhosis :how to manage leaky gut and endotoxaemia. World J Hepatol 2015; 7:425-42.

[53] JuC,Tacke F. Hepatic Macrophages in homeostasis and -liver diseases:from pathogenesis to novel therapeutic strategies. Cell Mol Immunol 2016;13: 316-27.

[54] Chakaroun RM,Massier L,Kovacs P.Gut microbiome, intestinal permeability - and tissue bacteria in metabolic disease:perpetrators or bystanders? Nutrients -2020;12:1082.

[55] Carpino G,Del Ben M,Pastori D,Carnevale R,Baratta F,Overi D, -etal .Increased liver localization of lipo-

 DOI: https://doi.org/10.30564/jer.v3i2.3520

polysaccharides in human and experimental NAFLD. Hepatology 2020;72: 470-85.

[56] Harte AL,Da Silva NF,Creely SJ,McGeeKC,Billyyard T,Youssef-Elabd EM, -etal .Elevated endotoxin levels in non alcoholic fatty liver disease.J Inflamm2010;7:15.

[57] Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(7):1761-72.

[58] Kudo H,Takahara T,Yata Y,Kawai K,Zhang W,Sugiyama T. Lipopolysaccharides triggered TNFα-induced apoptosis in murine model of non alcoholic steatohepapititis model.J Hepatol 2009;51:168-75.

[59] Ma J,Zhou Q,Li H. Gut microbiota and Nonalcoholic fatty liver disease:insights on mechanisms and therapy. Nutrients -2017;9:1124.

[60] Jin C,Engstler AJ,Ziegenhardt D,Bishoff SC,Trautwein C.Bergheim I.Loss of -lipopolysaccharides binding protein attenuates -the development of diet induced - non alcoholic fatty liver disease in mice.J Gastroenterol Hepatol -2017;32:708-15.

[61] Lawrence T.The nuclear factor κB pathway in inflammation.Cold Spring HarbaPerspect Biol 2009;1:a001651.

[62] Lancaster GI,Langley KG,Berglund NA,Kammoun HL,Reibe S,EstevezE, et al.Evidence that TLR4 is not a receptor for saturatedfatty acids but mediates lipid-induced inflammation by reprogramming -macrophagemetabolism. Cell Metab 2018;27:1096-110.

[63] Sumida Y,Yoneda M.Current -and future Pharmacologic therapies for NAFLD/ NASH. J Gastroenterol -2018;27:1096-110.

[64] Masarone M,RosatoV,DallioM,Gravina AG,Aglitti A,LoguercioC, et al.Role of Oxidative stress in the pathogenesis of NAFLD. Oxid Med Cell Longev -2018;2018:9547613.

[65] Simoes ICM,Fontes A,Pinton P,Zischka H,WieckowskiMR. Mitochondria in non alcoholic fatty liver disease. Int J Biochem Cell Biol 2018;95:93-99.

[66] Serfaty L,Lemoine M.Definition and natural history of metabolic steatosis: Clinical aspects of NAFLD, NASH and cirrhosis. Diabetes -Metab -2008;34:634-37.

[67] Palmieri B,SblendorioV. Oxidative stress detection:what for ?Part II.Eur Rev Med Pharmacol Sci2007;11:27-54.

[68] Forrester SJ,Kikuchi DS,Hernandes MS,XuQ,Griendling KK. Reactive oxygen species in Metabolic -and -inflammatorysignaling.Circ Res 2018;122:877-902.

[69] Chen Z,Tian R,She Z,Cai J,LiH. Role of Oxidative stress in the pathogenesis of NAFLD.. Free Rad Biol Med -2020;152:116-41.

[70] Thuy LTT,Hai H,Kawada N.Role of cytoglobin ,a novel radical scavenger -in stellate cell activation and hepatic fibrosis -.Clin Mol Hepatol 2020; 26:280-93.

[71] Ilyasova D,Scarborough P,Spasojevic I.Urinary biomarkers of Oxidative stress. Clin Chim Acta 2012;7:219-27.

[72] Damiano S,Sozio C,La Rosa G,Santillo M.NOX dependent signaling dysreulation in severe COVID -19. Clues to effective treatment.Front -Cell Inf -Microbiol -2020; 10:608435.

[73] Angelico F,Loffredo L,Pignatelli P,Augelletti T,Carnevale R,Pacella A, et al. Weight loss is associated -with -improved endothelial dysfunction via NOX2 –generated Oxidative stress down regulation in patients with Metabolic Syndrome.Intern Energ -Med -2012;7:219-27.

[74] Del Ben M,Polimeni L, Carnevale R,Bartimoccia S,Baratta F,Nocella C, et al. NOX2 –generated Oxidative stress is associated -with - severity of ultrasound -liver steatosis - inpatients with -non alcoholic fatty liver disease.BMC Gastroenterol -2014;14:81.

[75] Dong Y,Yuan Y.Accelerated inflammation and Oxidative stressinduced by LPS in acute lung injury.:inhibition by ST1926. Int J Mol Med -2018;41(5):3405-21.

[76] Loffredo L,Zicani AM,Perri L, Carnevale R,Nocella C, Angelico F, et al.Does Nox2 over activation in children with Nonalcoholic fatty liver disease? Antioxid -Redox Signal -2019;30:1325-330.

[77] Kim SY, Jeong JM,Kim SJ,Seo W, Kim MH,Choi WM, et al. Proinflammatory Hepatic Macrophages generate ROS -through NADPH-oxidase -via endocytosis of -monomeric - TLR4-MD2 complex.Nat Commun2017 ;8:2247.

[78] Buzzzetti E, Pinzani M, Tsochatzis EA . The multiple hit pathogenesis of Nonalcoholic fatty liver disease (NAFLD). Metab Clin Exp 2016; 65: 451-64.

[79] Chalasani N, Younossi ZM, Lavine AE, Diehl AM,Brunt EM,Cusi K, et al. American Gastroenterological - Association, American -Association for thestudy of - Liver disease, American -Association forGastroenterology;The diagnosis and management of -non alcoholic fatty liver disease:practice guidelines -by the American Gastroenterological - Association, American -Association for thestudy of - Liver disease, American -Association forGastroenterology. Gastroenterology 2012;142:1592-609.

[80] Tziomalos K,Athyros VG,KaragiannisA. Nonalco-



DOI: https://doi.org/10.30564/jer.v3i2.3520

holic fatty liver disease in type2 Diabetes: pathogenesis -and treatment options. -Curr Vasc Pharmacol -2012;10:162-72.

[81] Kulvinder Kochar Kaur, Gautam Allahbadia, Mandeep Singh . 'Attempt to utilize Classification of Type2 Diabetes mellitus subgroups provided by Ahlqvist to generate individualized treatment methods based on the actions on insulin resistance & βcell function :A move forward to more effective diabetes control from start &avoid End StageDamage ''.2021 Under review.

[82] Dasarathy S, Dasarathy J,Khayami A,Yerian LM,Sergent R,McCollough AJ. Randomized controlled trial -of omega3 fatty acids -in the - treatment - of non alcoholic steatohepapititis -in type2 Diabetes mellitus. Hepatology 2013; 58:518a.

[83] Alam F,Islam MA,Mohammed M,Ahmad I,Kamal MA,Donelly R, et al. Efficacy and safety of Pioglitazone monotherapy in type2 Diabetes mellitus.:a systematic review and -meta-analysis of Randomized controlled trials.Sci Rep -2019;9:5389.

[84] Lebovitz HE. Thiazolidenediones :The forgotten Diabetic medications .Curr -Diab Rep 2019;19:151.

[85] Schernather G,Currie CJ, Schernather GH.Do we still need Pioglitazone for the treatment - of type2 Diabetes mellitus?a risk benefit critique in 2013. Diabetes Care 2013; 36:S155-S161.

[86] Vieira R,Souto SB,Sanchez-Lopez E,Machado AL,Severino P,Jose S, et al. Sugar lowering drugs for -type2 Diabetes mellitus and Metabolic Syndrome-review of classical and newcompounds. Pt1-Pharmaceuticals -2019;12:152.

[87] Tyagi SM,Gupta P,Sai niAS,Kaushal C,Sharma S.The Peroxisome Proliferator adenineActivated Receptor:a family of nuclear -Receptors --role in various diseases.J Adv Pharm Technol Res 2011;2:236-40.

[88] Choi SS,Park J, Choi JH.Revisiting PPAR -γ -as a target -for the treatment of Metabolic disorders .BMB Rep - -2014;47:599-608.

[89] Fonseca V.Effect of thiazolidenediones on body -weight -in patients type2 Diabetes mellitus.Am J Med -2003;115:42S-48S.

[90] Kang JG,Park CY.The actions of -PPAR -γ -agonists on the various -target organs .Korean J Obes -2011;20:161-69.

[91] Kawai T,Funae O,Shimada A,Tabata -M,Hirata T,Atsumi Y, et al. Effects of pre treatment with low dose metformin on metabolic - parameters and -weight gain by -Pioglitazonein Japanese -patients -with type2 Diabetes.Int -Med -2008;47:1181-188.

[92] Musso G,Cassander M,Paschetta E,Gambino R. Thiazolidenediones and advanced liverfibrosis -in non alcoholic steatohepatitis -:a meta-analysis.JAMA Int -Med -2017;177:633-40.

[93] Bril F,Kalavalapalli S,Clark VC,Lomonaco R,Soldevila-Pico C,Liu IC, et al.Response to Pioglitazonein - patients -with -non alcoholic steatohepatitis - with vs without type2 Diabetes. Clin Gastroenterol Hepatol -2018;16:558-66.

[94] Yuan G,Zhang ML,Gong ZJ.Effects of PPAR –g agonist Pioglitazoneon rat -hepatic fibrosis. World JGastroenterol2004;10:1047-51.

[95] Shah RA,Kowdley KV. Obeticholic acid for the treatment of non alcoholic steatohepapititis.Expert Rev Gastroenterol Hepatol -2020;14:311-21.

[96] Verbeke L,Mannaerts I,Shierwagen R,Govaore O,Klein S,Vander Elst I, et al.FXR against Obeticholic acid reduces -hepatic inflammation and fibrosis in a rat model of toxic cirrhosis. Sci Rep -2016;6:33453.

[97] Li T,Francl JM,Boehme S,Chang JY. Regulation of cholesterol and Bile acid homeostasis by the cholesterol7α hydroxylase / steroid -response -element binding protein 2/micro RNA-33a in mice. Hepatology 2013; 58:1111-121.

[98] Pelliciari R, Costantino G, Camaioni E,Sadeghpour BM,Entrena A,Willson TM, etal . Bile acid derivatives -as ligands of the -Farsenoid X receptor:synthesis, evaluation and structure Activity relationship -of a series of body and side chain modified analogues -of -chenodeoxycholic acid. J Med Chem - -2004; 47:4559-69.

[99] Mudaliar S,Henry RR,SanyalAJ,Morrow L,Marshall HU,Kipnes M, etal .Efficacy and safety of the -Farsenoid X receptor agonist Obeticholic acid in patients -withtype2 Diabetes mellitus and -of -non alcoholic fatty liver disease. Gastroenterology -2013; 145:574-82.

[100] Hameed B, Terrault NA,Gill RM,Loomba R, Chalasani N,Hoofnage JH, etal .The NASH Clinical research network. Clinical and metabolic effects associated -with -weight changes -and - Obeticholic acid in non alcoholic steatohepatitis. Aliment -Pharmacol -Ther 2018;47: 645-56.

[101] Hindson J. Obeticholic acid for the treatment of non alcoholic steatohepapititis. Nat Rev Gastroenterol Hepatol 2020; 17:65.

[102] Berger J,Moller DE.The mechanisms of action of PPARs. Annu Rev Med -2002;53: 409-35.

[103] Connolly JJ,Ooka K,Lim JK,Future Pharmacotherapy -for non alcoholic steatohepapititis( NASH):review in phase 2 and 3 trials.J Clin Transl Hepatol

 DOI: https://doi.org/10.30564/jer.v3i2.3520

2018; 6:264-75.

[104] Pawlak M,Lefebvre P,Staels B. Molecular mechanisms of PPARα action and its impact on lipid metabolism , inflammation and fibrosis -in non alcoholic steatohepatitis. -J Hepatol 2015;62: 720-33.

[105] Musso G,Gambino R,Cassader M,Pagano G.A meta-analysis for the randomized -trials -for the treatment of non alcoholic -Fatty Acid Liver Disease. Hepatology 2010; 52:79-104.

[106] Bojic LA,Huff MW. Peroxisome Proliferator Activated Receptorδ:A multifaceted -metabolic player. Curr Opin Lipiodol 2013;24: 171-7.

[107] Karpe F,Ehrenborg EE.PPARδ in humans:genetic -and Pharmacologic evidence for a significant Metabolic -function. Curr Opin Lipiodol 2009;20: 333-6.

[108] Riserus U,Sprecher D,Johnson T,Olson E,Hirschberg S,Liu A, etal. Activation of Peroxisome Proliferator Activated Receptorδ( PPAR -δ)promotes reversal of multiple metabolic abnormalities ,reduces Oxidative stress,and increases fatty acid oxidation in moderately obese men. Diabetes 2008;57: 332-9.

[109] Ratziu V,Harrison SA,Francque S,Bedossa P,Lahert P,Serfaty L, etal .GOLDEN 505 Investigator Study Group. Elafibranor,an agonist of -the Peroxisome Proliferator Activated Receptor α,and δ induces resolution of non alcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016; 150:1147-59.

[110] Briand F,Heymes C,Bonada L,Angles T,Charpentier J,Branchereau M, etal.A 3week non alcoholic steatohepapititis mouse model -shows Elafibranor benefits -on hepatic inflammation and cell death. Clin Transl Sci 2020; 13:529-38.

[111] Tolbol KS,Kristiansen MN,Hansen HH,Veidal SS,Rigbolt KT, etal. Metabolic and hepatic effects of Liraglutide, Obeticholic acid and Elafibranor in diet induced obese -mouse model of biopsy confirmed non alcoholic steatohepatitis. -World JGastroenterol2018;24:179-94.

[112] Briand F,Maupoint J, BrousseauE,Breyner N,Bouchet M,Costard C, etal. Elafibranor improves diet induced non alcoholic steatohepatitis associated -with heart failure with preserved ejection fraction -in golden Syrian hamsters. Metabolism 2021; 117:154707.

[113] Cariou B,Hanf R,Lambert –Porcheron S,Zair Y,Sauvinet V, etal.Dual Peroxisome Proliferator Activated Receptor α,and δ agonist GFT505 improves hepatic and peripheral insulin sensitivity in abdominally obese -subjects. Diabetes Care 2013; 36:2923-930.

[114] Cariou B, Zair Y,Staels B,Bruckert E. Effects of -the new dual PPARα / δ agonist GFT505 on lipid and glucosehomeostasis in abdominally obese -patients with combined dyslipidemia or impaired glucose metabolism. Diabetes Care 2011; 34:2008-14.

[115] Jeong SW. Non alcoholic fatty liver disease:A Drug revolution is coming. Diabetes Metab J 2020;44:640-57.

[116] Irruarrizaga-Lejarreta M,Varela –Rey M, Fernandez-RamosD, Martinez-A rranz I,Delgado TC, etal. Role of Aramchol in steatohepapititis and - -fibrosis in mice . Hepatol Commun2017;1: 911-27.

[117] Dobrzyn A,Ntambi JM. Stearoyl-Co A Desaturase as a new drug for obesity treatment. ObesRev 2005;6:169-74.

[118] Goldiner I,Van der Velde AE,Vandenberghe KE,Van wijland MA,Halpern Z,Gilat T, etal.ABCA1 – dependent but apoA1 independent - cholesterol efflux -mediated by fatty acids -bile acid conjugates(-FABACs).Biochem J 2006;396:529-36.

[119] Safaldi K,Konikoff FM,Mahmaid M,Zelber –Sagi S,Halpern N,Gilat T etal.The fatty acids -bile acid conjugate Aramchol reduces liver fat content in Non Alcoholic Fatty Acid Liver Disease. Clin Gastroenterol Hepatol 2014; 12:2085-91.

[120] Gentiella R,Pechtner V,Corcos A,Consoli A. Glucagon like peptide 1 receptor -agonists in type2 -Diabetes treatment :are they all the same? Diabetes -Metab Res Rev 2019; 35:e3070.

[121] Greiner TU,Backhed F.Microbial regulation of GLP-1 and L-cell biology . -Mol Metab 2016;15:753-58.

[122] Michalowska J,Miller-Kasprzak E,Bogdanski P. Incretin -hormones in obesity -and related cardiometabolic disorders;the Clinical perspective. Nutrients -2021;13:351.

[123] Armstrong MJ,Gaunt P,Aithal GP,Barton D,Hull D,Parker R, etal .LEAN trial team .Liraglutidesafety and efficacy in for patients with non alcoholic steatohepatitis(LEAN):a multicenter ,double blinded , a -randomized,placebo- controlled -phase 2 -study . Lancet 2016; 387:679--90.

[124] DeFronzo RA,Ratner R,Han J,Kim D,Fineman M etal. Effects of Exenatide ( Extendin-4)on glycemic control and weight control over 30weeks in metformin treated patients with type2 - Diabetes. Diabetes Care 2005; 28:1092-100.

[125] Crane J,McGowan B.The GLP-1 agonists, Liraglutide,as a pharmacotherapy for obesity.Ther Adv Chronic Dis - 2016; 7:92-107.



DOI: https://doi.org/10.30564/jer.v3i2.3520

[126] Davies MJ,Aronne LJ,Caterson ID,Thomsen AB,Jacobsen PB,Marso SP. Liraglutide and cardiovascular outcomes -in adults for obesity:a posthoc analysis from the SCALE -Diabetes randomized controlled trials. Diabetes Obes Metab 2018;20:734-39.

[127] AdamsJM,Pei H,Sandoval DA,SeelyRJ,Chang RB,-Liberles SD, etal. Liraglutide modulates appetite and body weight through Glucagon like peptide 1 receptor -expressing glutamatergic neurons. Diabetes -2018;67:1538-48.

[128] Mantovani A,Petracca G,Beatrice G,Csermely A,Lonardo A,Targher G. Glucagon like peptide 1 receptor -agonists for treatment of Non Alcoholic Fatty Acid Liver Disease and Non Alcoholic steatohepapititis:an updated meta-analysis of randomized controlled trials. Metabolites -2021;11:73.

[129] Kapodistria K,Tsilibary EP,KotsopouloE,Moustardas P,Kitsiou P. Liraglutide,A human Glucagon like peptide 1 analogue ,stimulates AKT dependent -survival signaling.J Cell Mol Med 2018;22:2970-980.

[130] HeQ,Sha S,Sun L,Zhang J,Dong M. GLP-1 analogueimproves - hepatic lipidaccumulation by inducing -autophagy via AMPK/ mTOR pathway. Biochem -Biophys Res Commun -2016;476:196-203.

[131] Chalasani N, Younossi ZM, Lavine AE, Diehl AM,Brunt EM,Cusi K,Sanyal AJ. The diagnosis and management of -non alcoholic fatty liver disease:practice guidelines -by the American Gastroenterological - Association, American -Association for thestudy of - Liver disease, American -Association forGastroenterology. Hepatology 2012;302:G225-G235.

[132] Nelson CH,Etchevers K,Yi S,Breckenridge D,Hepner M,Patel U etal.Pharmacokinetic ,safety and tolerability of Selonsertib,an apoptosis signal regulating kinase 1(ASK1) Inhibitor), following first -in human single and multiple ascending doses in healthy subjects.Clin Pharmacokinet 2020;59:1109-17.

[133] Budas G,Karnic S,Johnson T,Shafideh T,Watkins S , Breckenridge D, etal. Reduction of Liver steatosis and fibrosis -with an ASK1 Inhibitor in murine model of NASH is accompanied by improvements in cholesterol, the bile acid and lipid metabolism.J Hepatol -2016;64:S170.

[134] Loomba R, Lawitz EJ,Mantry PS, Jayakumar A, Caldwell SH,Arnold H etal.The - ASK1 Inhibitor Selonsertib in - patients with Non Alcoholic steatohepapititis:a randomized phase 2 - trial. Hepatology 2018;67:549-59.

[135] Dickson I.No antifibrotic effects of Selonsertib in NASH. Nat Rev Gastroenterol Hepatol 2020; 17:260.

[136] Puente A,Fortea JL,Cabezas J,Arias Loste MT,Iruzubieta P,Llerena S, etal.LOXL2;A new target in antifibrogenic therapy. Int J MolSci 2019;20:1634.

[137] Rodriguez HM,Vaysberg M,Mikels A,McCauley S,Velayo AC,Garcia C, etal.Modulation of lysyl oxidase –like 2 enzymatic activity by an allosteric antibody Inhibitor.J Biol Chem 2010;285:20964-20974.

[138] Lipson KE,Wong C,Teng Y,Spong S.CTGF is a central mediator of tissue remodeling and its inhibition can reverse the fibrosis.Fibrogenesis T issue Repair 2012;5:S 24.

[139] Harrison SA, Abdelmalek MF, Caldwell SH,Shiffman ML, Diehl AM,Ghalib R etal.Simutuzumab -is ineffective for patients with bridging fibrosis or compensated cirrhosis caused by ) -non alcoholic steatohepapititis. Gastroenterology 2018;155:1140-53.

[140] Marra F, Tacke F.Roles of chemokines - in liver disease. Gastroenterology 2014;147:577-94.

[141] Kim BM,Abdelfattah AM,Vasan R,Fuchs BC,Choi MY. Hepatic Stellate cells -secrete Cc15 to induce hepatic steatosis.Sci Rep 2018;8:7499.

[142] Friedman SL, Sanyal AJ, Goodman SM, Lefebvre E,Gottwald M,Fischer L, Ratziu V.Efficacy and safety -study of cenicriviroc for treatment of -non alcoholic steatohepatitis in adult subjects with Liver fibrosis:CENTAUR Phase 2b study design.Contemp Clin Trials2016; 47:356-65.

[143] Friedman SL, Ratziu V,Harrison SA, Abdelmalek MF, Aithal GP,Caballeria J, etal .A randomized,placebo- controlledtrial of cenicriviroc for the treatment of -non alcoholic steatohepatitis with fibrosis. Hepatology 2018; 67:1754-67.

[144] Anstee QM,Neuschwander –Tetri BA,Wong VW, Abdelmalek MF, Younossi ZM,Yuan J, etal. - Cenicriviroc for the treatment of -liver fibrosis in adults with - of -non alcoholic steatohepatitis:AURORA phase 3 -study design. Contemp Clin Trials2020; 89:105922.

[145] Boutari C,Perakakis N,Mantzoros CS. Association of Adipokines with development of , non alcoholic fatty liver disease.Endocrinol Metab 2018;33:33-43.

[146] Polyzos SA,Kountouras J, Mantzoros CS.Leptin in non alcoholic steatohepatitis:a narrative review. Metabolism -2015;64:60-78.

 DOI: https://doi.org/10.30564/jer.v3i2.3520

[147] Jamali R,Arj A,Razavizade M,Aarabi MH.Prediction of non alcoholic fatty liver disease via a novel panel of serum Adipokines.Medicine -2016;95:e2630.

[148] Polyzos SA,Kountouras J,Anastasilakis AD,Geldari EV, Mantzoros CS. Irisin in -patients -with -non alcoholic fatty liver disease . Metabolism -2014;63:207-17.

[149] Zhang SR,Fan ZM. Ghrelin- ghrelin-O-Acetyl transferase system -in the pathogenesis of non alcoholic fatty liver disease. World J Gastroenterol2015;21:3214-22.

[150] Arvaniti VA,Thomopoulos KC,Tsamandas A,Makri M,Psyrorogiannis A,Vafiadis G, etal .Serum adiponectin -levels in different types of non alcoholic fatty liver disease: correlation with - -steatosis,necro inflammation and -fibrosis.Acta Gastroenterol Belg -2008;71:355-60.

[151] Garinis GA,Fruci B,Mazaa A,DeSienna M,Abenavoli A,Gulletta E, etal.Metformin -versus dietary -treatment of -non alcoholic steatohepatitis.Int J Obes -2010;34:1255-64.

[152] Ryan MJ,Dudash HJ,Docherty M,Geronilla KB,-Baker BA,Haff GG, etal. Vitamin E and Csupplementation -reduces Oxidative stress improves antioxidant tenzymes -and positive muscle work -in chronically loaded muscles -of aged rats .Exp Gerontol -2010;45:882-95.

[153] Balmer ML,Siegrist K,Zimmermann A,Dufour JF.Effect of ursodeoxycholic acid in combination with Vitamin E on Adipokines and apoptosis in patients with non alcoholic steatohepatitis. Liver Int -2009; 29:1184-88.

[154] Otabe S,Yuan X,Fukutani T,Wada N,Hashinaga T,Nakayama H, etal.Over expression of human -adiponectin -in transgenic mice - results in suppre ssion of fat accumulation and prevention of premature death -by high calorie diet. Am J Physiol Endocrinol Metab -2007;293:E210-E218.

[155] Sharma D,Wang J,Fu PP, Sharma S,Nagalingam A,Mells A, etal. Adiponectin antagonizes the oncogenic actions of leptin in Hepatocellular carcinogenesis. Hepatology 2010; 52:1713-22.

[156] Kelesidis T, Kelesidis I,Chou Z, Mantzoros CS.Narrative review:The role of leptin in human -physiology:emerging Clinical applications .Ann Intern Med 2010;152:93-100.

[157] Unger RH.Lipotoxic diseases, Annu -Rev Med 2002;53:319-36.

[158] Ikejima K,Honda H,Yoshikawa M,Hirose M,Kitamura T,Takei Y, etal.Leptinaugments inflammatoryand profibrogenic -responses in the murine liver induced by hepatoxic chemicals. Hepatology 2001; 34:288-97.

[159] Polyzos SA,Aronis KN,Kountouras J,Raptis DD,Vasiloglu MF, Mantzoros CS. Circulating leptin in non alcoholic fatty liver disease:a systematic review and -meta-analysis. Diabetologia --2016;59:30-43.

[160] Muse ED,Obici S,Bhanot S,Monia BP,McKay RA,Rajala MW, etal.Role of resistin -in diet induced hepatic insulin resistance.J Clin Invest -2004; 114:232-39.

[161] Bertolani C,Sancho Bru P,Failli P,Batallier R,Aleffi S,DeFranco R, etal. Resistin as an intra hepatic cytokine : Over expression during chronic injury and induction of proinflammatory action in -hepatic stellate -cells.Am J Pathol -2006; 169:2042-53.

[162] Jamali R, Razavizade M, Arj A,Aarabi MH. Serum adipokines might predict liver histology findings -in - non alcoholic fatty liver disease. World J Gastroenterol2016;22:5096-103.

[163] Rasouli N,Yao-BorengaaserA,Miles LM,Elbein SC,Kern PA.Increased plasma Adiponectin in response to Pioglitazone does not result from Increased gene expression . Am J Physiol Endocrinol Metab -2006;290:E42-E46.

[164] Delporte C. Structure -and physiological actions of -ghrelin.Scientifica 2013; 2013:518909.

[165] Purnell JQ,Weigle DS,Breen P,Cummings DE. Ghrelin levels correlate with insulinlevels, insulin resistance,and high density lipoprotein cholesterol ,but not with gender ,menopausal status -or cortisol -levels in humans. J Clin Endocrinol Metab -2003;88:5674-79.

[166] LiY,Hai J, Li L,Chen X,Peng H,Cao M, etal. Administration -of Ghrelin improves inflammation, Oxidative stress,and apoptosis during -and after non alcoholic fatty liver disease development.Endocrine 2013;43:376-86.

[167] Mao Y,Cheng J,YuF,LiH,GuoC,Fan X. Ghrelin attenuated lipotoxicity via autophagy induction .Cell Physiol Biochem -2015;37:563-76.

[168] Schnyder S,Handschin C. Skeletal muscle as an endocrine organ:PGC-1α,myokines and exercise.Bone -2015;80:115-25.

[169] Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Therapeutic Applications of the Recent Understanding of Brown or "Beige" Adipocyte Physiology. Adv Tech Biol Med -2015; 3: 128.
DOI: 10.4172/2379-1764.1000128.

[170] Zhang Y,Li R,Meng Y,LiS,Donelan W,Zhao Y,



DOI: https://doi.org/10.30564/jer.v3i2.3520

etal. Irisin stimulates browning of white adipocytes through -mitogen activated protein kinase p38MAP Kinase and ERKMAP Kinase Signaling. Diabetes -2014;63:514-25.

[171] Polyzos SA,Mathew H, Mantzoros CS. Irisin:A true, circulating hormone. Metabolism 2015;64:1611-18.

[172] Perez –Soleto D,Roca –RivadaA,BaamondeI,Baltar J,Castro AI,Dominguez E, etal.Lack of adipocytes-Fndc5/ Irisin expression -and secretion reduces thermogenesis and enhancesadipogenesis.Sci Rep -2017;7:16289.

[173] Muir AJ,Levy C,Janssen HLA,Montano-Loza AJ,-Shiffman ML, Caldwell S, etal. Simutuzumab for primary - sclerosing -cholangitis: phase 2 study results with insights -on the natural history of -disease. Hepatology 2019; 69:684-98.

[174] Chen P,Chung FM,Chang DM,Tsai JC,Huang HF,Shin SJ, etal.Elevated plasma levels of visfatin/ preB cell colony-enhancing factor in treated patients with type2 - Diabetes. -J Clin Endocrinol Metab -2006;91:295-9.

[175] Mousavi Z,Ganji A,Farrokh Tehrani D,Bahari A,Esmeil Zadeh A,Delghadi M. Correlation of visfatin-levels with non alcoholic fatty liver in Metabolic Syndrome.J Islam Republic Iran 2017;31:28.

[176] KadoglouNP, Tsanikidis H,Kapelozou A,Vrabas I,Vitta I,Krayannacos PE, etal.Effect of -ofrosiglitazone -and metformin treatment - on apelin, visfatin ghrelin levels in -patients with type2 - Diabetes .Metabolism 2010;59:373-79.

[177] Kim E,Voatour P. Hepatocellular carcinoma:Old friends and new tricks.Exp Mol Med2020; 52:1898-1907.

[178] CholankerilG,Patel R,,Khurana S,Satapathy SK. Hepatocellular carcinoma in non alcoholic steatohepatitis:current -knowledge and implications for management. World JHepatol 2017; 9:-533-43.

[179] Jing YY,Han Z,Sun K,Zhang SS,Hou J,Liu Y, etal. Toll like receptor 4 signaling promotes epithelial –mesenchymal transition in human - Hepatocellular carcinoma induced by lipopolysaccharides.BMC Med 2012;10:98.

[180] Li H, Li Y, LiuD, LiuJ.LPS promotes epithelial –mesenchymal transition and activation of -TLR4/ JNK signaling.Tumor -Biol -2014;35:10429-35.

[181] Gupta H,Youn GS,Shin MJ,Suk KT. Gut microbiota in Hepatocarcinogenesis. Microorganisms -2019;7:121.

[182] Saxena NK,FuPP,Nagalingam A, Wang J,Handy J,Cohen C, etal. Adiponectin modulates -c –jun N terminal kinase -and mammalian target of rapamycin -and inhibits Hepatocellular carcinoma. Gastroenterology -2010;139:1762-73.

[183] Al-Gayyar AM,Abbas A,Hamdan AM.Chemopreventive -and hepatoprotective -role of Adiponectin(SULF2 Inhibitor) in Hepatocellular carcinoma. Biol Chem 2016;397:257-67.

[184] Kamada Y,Matsumoto H,Tamura S,Fukushima J,Kiso S,Fukui K, etal.Hypo Adiponectinemia accelerates hepatic tumorformation - -in non alcoholic steatohepatitis mouse model.J -HepatoL -2007;47:556-64.

[185] Shen J,Yeh CC,Wang Q,Gurvich I,Siegel AB, etal. Plasma Adiponectin and Hepatocellular carcinoma survival -among patients without liver transplantation.Anticancer Res 2016;36:5307-14.

[186] Wei R,Hu Y,Dong F,Xu X,Hu A,Gao G. Hepatoma -cell-derived leptin down regulates -the immunosuppressive function of regulatory T cells -to enhance the anti tumor activity of CD 8+T cells -.Immunol Cell Biol -2016;94:388-99.

[187] Stefanou N,Papanilkolaou V,Furukawa Y,Nakamura Y,Tsezou A. Leptin as acritical regulator of Hepatocellular carcinoma development through modulation of human telomerase -reverse transcriptase. BMC Cancer -2010;10:442.

[188] Levielle M,Estall JL. Mitochondrial dysfunctionin the transition - from -NASHto HCC. Metabolites -2019;9:233.

[189] Nakagawa H,Umemura A,Taniguchi K,Font –Burgada J,Dhar D,Ogata H, etal.ER Stress -cooperates with hypernutrition to trigger TNF dependent -spontaneous HCC development. Cancer Cell -2014;26:331-43.

[190] Von Loeffelholz H,Horn P,Birkenfeld AL,Claus RA,Metzing BU,Docke S, etal.Predictor of liver fat -in preoperative patients with non alcoholic fatty liver disease. J Invest Surg -2016;29:266-74.

[191] Peter A,Kovarova M,Staiger H,Mechann J,Schick F,Konigsrainer A, etal.The Hepatokines Fetuin A and -Fetuin B -are upregulated in the state of hepatic steatosis and may differently impact -on glucose-homeostasis in humans. Am J Physiol Endocrinol Metab -2018;314:E266-E273.

[192] Cui Z,Xuan R,Yang Y.Serum Fetuin A level is associated -with non alcoholic fatty liver disease in Chinese population.Oncotarget -2017; 8:-107149-107156.

[193] Mukhuty A,Fouzder C,Mukherjee S,Malick C,Mukhopadhyay S,Ray S, etal. Fetuin A secretion from Pancreatic βcells - -adversely affects -its function and elicits inflammation. Biochem -Biophys Res

 DOI: https://doi.org/10.30564/jer.v3i2.3520

Commun -2017;491:1118-24.

[194] -Dasgupta S,Bhattacharya S,Biswas A,Majumdar SS, Mukhopadhyay S,Ray S, etal. -Nuclear factor kappa Bmediates -lipid-induced Fetuin A expression in hepatocytes -that improve adipocyte -function effecting insulin resistance.Biochem J -2010;429:451-62.

[195] Mori K,Emoto M, Araki T,Yokoyama H,LeeH ,Taramura M, etal. -Effects of Pioglitazone on Serum Fetuin A levels -in -patients with type2 - Diabetes. Metabolism 2008;57:1248-52.

[196] Ochi A, Mori K,Emoto M, Nakatani N, Morioka T,Motoyama K, -etal.Direct inhibitory -Effects of Pioglitazone on -hepatic -Fetuin A expression.PLoS One -2014;9:e88704.

[197] Li L,Gu X,Fang M,JiJ,YiC,Gao C.The diagnostic value of Serum fucosylated Fetuin A in hepatitis Bvirus related liver diseases. Clin - Chem LabMed -2016;54:693-701.

[198] Pan X,Kaminga AC,Chen J,Luo M, LuoJ. Fetuin A and -Fetuin B - in non alcoholic fatty liver disease:a meta-analysis and -meta regression. Int JEnviron Res -Public Health2020;17:2735.

[199] Meex RC,Hoy AJ,Morris A,Brown RD,LoJC,Burke M, etal. -Fetuin B -is a -secreted hepatocyte factor -linking steatosis to impaired glucose metabolism. Cell Metab 2015;22:1078-89.

[200] Zhou W, Yang -J,Zhu J, Wang -Y,Wu Y,Xu L, etal. -Fetuin B - aggravates -liver X receptor mediated -hepatic steatosis -through AMPK in Hep G2 cells in mice .Am J Transl Res -2019;11:1498-1509.

[201] Ebert T,Linder N,Schaudinn - A,Busse H,Berger J,Lichtinghagen R, etal. -Association of -Fetuin B - with markers of liver fibrosis in non alcoholic fatty liver disease .Endocrine 2017;58:246-52.

[202] Zhong G,Kirkwood J,Won KJ,Tjota N,Jeong H,Isoherranen N. Characterization of Vitamin A metabolome -in human livers with and -without non alcoholic fatty liver disease.J Pharmacol -Exp Ther 2019;370: 92-103.

[203] Perduca M,Nicolis S.Mannuci B,Galliano M,Monaco HL.Human plasma Retinol Binding protein -4(RBP4) is also a fatty acid Binding protein. Biochim -Biophys Acta Mol Cell Biol Lipids 2018;1863:458 -66.

[204] Wang X,Chen X, Zhang H,Pang J,Lin J, Xu X, etal. Circulating -Retinol Binding protein 4is associated -with development -and regression of non alcoholic fatty liver disease. Diabetes Metab 2020;46: 119-28.

[205] Graham TE, Yang Q,Bluher M,Hammarstedt A,Ciaraldi TP,Henry RR, etal. Retinol Binding protein 4 and insulin resistance in lean ,obese and diabetic -subjects. NEngl J -Med 2006;354:2552-63.

[206] Petta S,Tripodo C,Grimaudo S,Cabibi D,Camma C,DiCristina A, etal.High liver RBP4 protein content -is -associated -with histological features in patients with genotype1 chronic hepatitis C and with non alcoholic steatohepatitis. Dig -Liver Dis -2011;43:404-10.

[207] Bahr MJ,Boeker KH,Manns MP,Tietge UJ.Decreased hepatic - RBP4 -secretion -is correlated with - -reduced levels -hepatic - glucose -production but is not -associated -with insulin resistance in patients with cirrhosis.Clin -Endocrinol -2009;70:60-5.

[208] Hara H,Uchida S,Yoshi mura H.Aoki M,Toyoda Y,Sakai K, etal.Isolation and -Characterization ofa novel liver specific gene, Hepassocin,upregulated -during liver regeneration. Biochim -Biophys Acta -2000;1492:31-44.

[209] Abdelmeomen G,Khodeir S,Zaki AN,Kasaab M,Abou Saif S,Abd Elasam S.Over expressionof -Hepassocin in diabetic -patients with non alcoholic fatty liver disease may facilitate increased -hepatic lipid accumulation. Endocrin Metab Immune Disord Drug Targets - 2019;19: 185-8.

[210] Wu HT,Lu FH,OuHY,Su YC,Hung HC, Wu JS, etal. The role of Hepassocin in the development of non alcoholic fatty liver disease. -J Hepatol 2013;59: 1065-72.

[211] Cheng KP, OuHY, Hung HC,LiCH,Fan KC, Wu JS, etal. Unsaturated fatty acids increase the expression of Hepassocin through a Signal -Transducers and Activators of Transcription3 dependent pathway in HepG2 cells.Lipids - 2018;53:863-69.

[212] Jung TW, Chung YH,Kim HC, Abd -El-Aty AM, Jeong JH.Hyper lipidemia-induced -Hepassocin in the liver contributes -to insulin resistance in skeletal muscle. - MolCell Endocrinol2018; 470:26-33.

[213] YuHT, Yu M,Li CY,Zhan YQ,Xu WX, Li -YH , etal. Specific - expression of -and regulation -of Hepassocin - in the liver and down regulation -of the correlation of -HNF1 alpha with decreased levels of Hepassocin in human Hepatocellular carcinoma. J Biol Chem 2009;284:133335-1313347.

[214] Li CY,Cao CZ, Xu WX, Cao MM, Yang F,Dong L, etal. Recombinant human -Hepassocin -stimulates -proliferation of hepatocytes -in vivo and improves survival -in -Hepatocellular carcinoma.Gut -2010;59:817-26.

[215] Yan J, Yu Y, Wang N, Chang Y,Ying H, Liu W, etal.



DOI: https://doi.org/10.30564/jer.v3i2.3520

LFIRE1/HFREP-1,a liver Specific - gene is frequently -down regulated and has growth suppressor activity in Hepatocellular carcinoma. Oncogene -2004;230:1939-49.

[216] Pan J,Parlee SD,Brunel FM, Li P,LuW,Perez-Tilve D, etal.Optimization of peptide inhibitors of β-Klotho as antagonists of Fibroblast -growth -factor 19 and -21.ACS Pharmacol Transl Sci -2020;3:976-86.

[217] Wu AL,Coulter S,Liddle C,Wong A,Eastham-Anderson J,French DM, etal.FGF19 regulates cell proliferation, glucose and bile acid metabolism via FGFR4 -dependent and independent pathways. PLoS One -2011;6:e17868.

[218] Jiao N,Baker SS,Chapa-Rodriques A, Liu W,Nugent CA,Tsompana M, etal.Suppressed hepatic bile acid signaling despite elevated production of primary -and secondary bile acids in NAFLD.Gut -2018;67:1881-91.

[219] Li Y,Zhang W,Doughtie A,Cui G, Li X,Pandit H, etal.Upregulation of Fibroblast -growth -factor 19 and its receptor associates -with -progression from -fatty liver to Hepatocellular carcinoma. Oncotarget -2016; 7:-52329-52339.

[220] Chen L, Liu H, Liu J,Zhu Y,Xu L,HeH, etal.Klotho endows hepatoma cells -with resistance to anoikis -via VEGFR 2/PAK1 activation in -Hepatocellular carcinoma. PLoS ONE -2013;8:e58413.

[221] Gong Q,HuZ, Zhang F,Cui A, Chen X,Jiang H, etal. Fibroblast -growth -factor 21 improves insulin sensitivity by inhibiting mammalian target of rapamycin complex1 in mice . Hepatology 2017; 64:425-38.

[222] Hong ES,Lim C,Choi HY,Lee YK.KuEJ,Moon JH, etal.Plasma of Fibroblast -growth -factor 21 levels increase with ectopic fat accumulation -and its receptor levels -are decreased in the visceral fat of in -patients with type2 - Diabetes .BMJ Open Diabetes Res Care 2019;7:e00076.

[223] Flisiak-IackiewiczM, Bobrus-Chociej A, Wasilewska M, Tarasow E,WojtowskaM, Lebenszejn DM. Can Hepatokines be regarded as novel noninvasive serum biomarkers -of intraHepatic liver -content in obese -children?Adv Med Sci -2019;64:30484.

[224] Rusli F,Deelen J,Andriyani E,Boekschoten MV,Lute C,Van den Akker EB, etal. Fibroblast -growth -factor 21 reflects liver fat accumulation - and dysregulation of signaling pathways in the liver -of C57BL/6J mice.Sci Rep - 2016; 6:30484.

[225] Yang M,Xu D, Liu Y,Guo X, Li W, Guo C, etal. Combined serum -biomarkers in noninvasive -diagnosis of non alcoholic steatohepapititis. PLoS ONE -2015;10:e131664.

[226] Yang C, Lu W,Lin T,You P,YeM,Huang Y, etal. Activation - of liver FGF21 -in Hepatocarcinogenesis and during Hepatic stress .BMC -Gastroenterol 2013; 13:67.

[227] Kong FJ,MaLL,LiG,Chen YX,Zhou JQ,Circulating betatrophin levels an d gestational Diabetes mellitus:a systematic review and -meta-analysis -. PLoS ONE -2017;12:e016994.

[228] Lee YH, Lee SG, Lee CJ,Kim SH,Song YM,Yoon MR, etal. Association between betatrophin/ ANGPTL8 and non alcoholic fatty liver disease:animal and human studies. Sci Rep - 2016; 6:24013.

[229] Zhang R.The -ANGPTL3-4-8 model ,a molecular -mechanism for triglyceride trafficking .Open Biol -2016; 6:150272.

[230] Yin Y,Ding X,Peng L,Hou Y,Ling Y,GuM, etal.Increased serum ANGPTL8 concentrations in patients -with pre Diabetes and -type2 - Diabetes.J Diabetes Res 2017; 2017:8293207.

[231] Gusarova V,Alexa CA,Na E,Stevis BE,Xin Y,-Bonner-Weir S, etal. ANGPTL8/ betatrophin does notcontrol Pancreatic βcells - expansion.Cell -2014; 159:691-6.

[232] Zhang L,Shannon CE, TM,Abdul –Ghani MA,-Fourcaudot M,Norton L.Regulation of ANGPTL8 in liver -and adipose tissue by nutritional and hormonal signals and the effect on glucosehomeostasis in mice. Am J Physiol Endocrinol Metab -2020;318:E613-E624.

[233] Chen YQ,Pottanat TG,Siegel RW,Ehsani M,Qian YQ,Zhen EY, etal. Angiopoietin –Like Protein- 8 differentially regulates ANGPTL 3 and ANGPTL 4 during postprandial -partitioning of fatty acids.J Lipid Res - 2020;61:1203-20.

[234] Dijk W,Kersten S.Regulation of -Lipid metabolism by Angiopoietin –Like Protein's . Curr Opin Lipiodol 2016;27: 249-56.

[235] Yoshida K,Shimizugawa T,Ono M,Furukawa H. Angiopoietin –Like Protein 4 is a potent hyperlipidemia-inducing factor in mice and inhibitor of lipoprotein lipase. J Lipid Res - 2002;43:1770-72.

[236] Ng KT,Xu A,Cheng Q,Guo DY,Lim ZX,Sun CK, etal. Clinical relevanc e -and therapeutic potential -of -Angiopoietin –Like Protein 4 in Hepatocellular carcinoma.Mol Cancer 2014;13:96.

 DOI: https://doi.org/10.30564/jer.v3i2.3520