LUPINE PUBLISHERS

Current Trends in Gastroenterology and Hepatology

DOI: 10.32474/CTGH.2020.03.000151

ISSN: 2641-1652

Review Article

Non-Alcoholic Fatty Liver Disease and its Interplay with Various Metabolic Disorders

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Received: February 20, 2020 **Published:** March 03, 2020

Abstract

Nonalcoholic fatty liver disease (NAFLD) is described as exposition of multiplex liver metabolic disturbance interconnected with obesity. NAFLD is depicted by steatosis, excessive accumulation of fats in liver, due to triglycerides export and oxidation of fatty acid from plasma and de novo synthesis. Hepatic steatosis can therefore be explained as biochemical outcome of inconsistency between interfused mechanisms of lipid biotransformation. This condition is allied to a range of various modifications in lipoproteins, fatty acids, and glucose metabolisms in organism. So, above metabolic disfunctions are suspected to be the origin of possibility for adverse cardiometabolic risk agents related to NAFLD, like dyslipidemia, Type 2 diabetes mellitus (T2DM), and insulin resistance. Reactive oxygen species (ROS) generation participates as known inducer of inflammation and oxidative stress, that exacerbate this disease. These disorders are hallmarks that worsen NAFLD complications, so far participate in developing advanced stages of NAFLD and incline the body to CVD and T2D. The reciprocal risks exist among these diseases. Given the sharp growing prevalence and persistence of NAFLD, and its complexity that provoke additional metabolic syndrome, this review discusses various mechanisms of developing NAFLD, interaction with other associated hallmarks, aiming to clarify beneficial mechanisms for improvement.

Keywords: Nonalcoholic fatty liver disease; oxidative stress; Type 2 diabetes; noncoding RNAs; cardiovascular disease

Introduction

The liver is known as metabolically complex organ due to its multiple biological activities, involving detoxification of various endogenous metabolites and exogenous toxic substances, formation of biochemicals needed for degradation and the synthesis of protein. The liver also serves an exigent task in metabolisms like lipid homeostasis and glycogen storage regulation [1]. Increased activity of mitochondria consequent to the fatty acids hyper-afflux from oxidation of fatty acid, produce free radicals that generate liver oxidative stress [2]. Abnormal function of liver may engender several metabolic impairments, such as NAFLD (Marrero et al., 2002). NAFLD is explained as the grouping of excess fat into liver cells, that does not result from alcohol consumption. The existence of fats in the liver is normal; however, if the concentration of fats exceeds 5%-10% of the weight of liver, then it is called a fatty liver (steatosis). Thus, NAFLD is explained as the amassing of liver fat of >5% of liver weight with <10g of daily alcohol consumption (Bayne, 2010). Besides these, generation of NAFLD was discovered to be linked with insulin resistance, the latter is known also as a critical risk factor for developing type 2 diabetes (T2D) [3]. NAFLD comprise a large spectrum of manifestations extending from simple steatosis, continuing to nonalcoholic steatohepatitis (NASH) and cirrhosis. Furthest, NAFLD correlates with significant higher risk of developing hepatocellular carcinoma (HCC) [4]. The worse hallmark of this disease is the significant interdependence with various attributes of metabolic syndrome (MetS), such (T2DM), obesity or dyslipidemia [5]. MetS is hallmarked by the aggregation of several impairments involving elevated blood pressure, obesity, dyslipidemia, insulin resistance and proinflammatory activities [6]. Moreover, studies by different researchers elucidated NAFLD as the leading inducer of liver diseases and the main reason for impaired liver function worldwide; also considered as an inherent

part of MetS (hypertension, hyperglycemia, central obesity and dyslipidemia) [7,8]. The evolution of MetS has been coincided with a growth in liver disorders including NAFLD, and was revealed to correspond with disorders, like cardiovascular disease (CVD). Particularly, NAFLD has been taken as hepatic exposition of MetS [9].

The NAFLD prevalence increases quickly around the world and noted as a camouflaged epidemic. The Universal estimation of NAFLD prevalence in general population has overpassed 25% [10], See Figure 1. In developing countries such as, China; and India, the number of NAFLD patients has been augmenting sharply over the last decades [11]. However, no medications presently approved for NAFLD. The primary therapeutic intervention in NAFLD, same as in other MetS is gained from lifestyle improvement, promoting equitable low-energy diet, together with promoting physical activity. So, these are prime remunerative approaches for this condition [12,13]. Lifestyle moderation has improved the metabolism syndrome features; however, more effort needs to be made in addressing various MetS components [14]. Thus, to provide better understanding that will help different players involved in management of MetS disorders. This review discusses various mechanisms of developing NAFLD and its interplay with other metabolic disorders, while clarifying beneficial mechanisms for improvement.

N. America; North America, S. America; South America, Euro; Europe, M. East; Middle East.

Figure 1: NAFLD Prevalence in global remarkable regions.

Prevalence of NAFLD

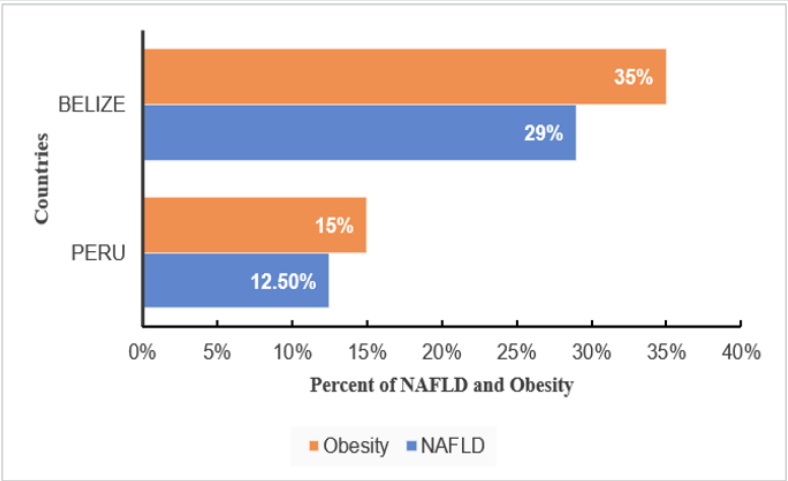
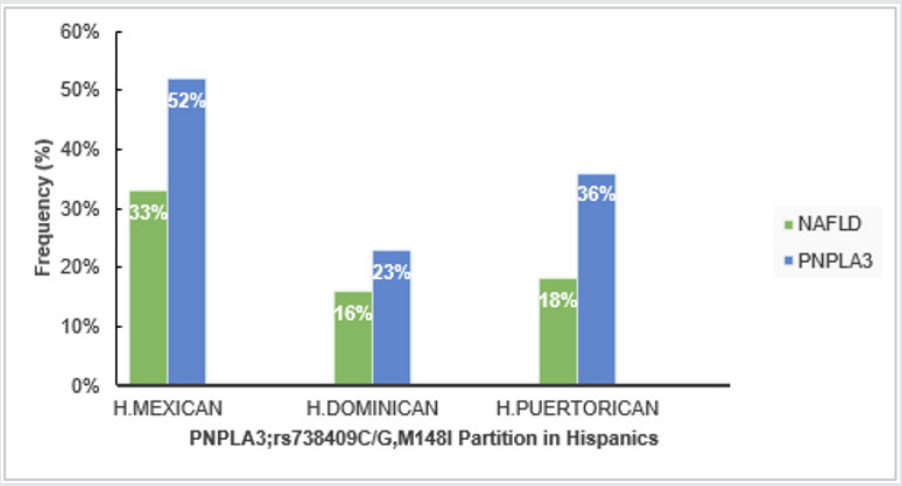


Figure 2: Influence of obesity on NAFLD.

The NAFLD prevalence increases quickly in every region in the world as a masked epidemic. The worldly estimation of NAFLD prevalence in general population has surpassed 25% [10] (Figure 2).

In region of South and Central America, NAFLD prevalence varies depending on obesity rate, where Belize has the highest obesity prevalence of 35% with NAFLD 29% and Peru has the lowest obesity prevalence of 15% with NAFLD 12.5% [10]. The

Occurrence of obesity aggravate NAFLD prevalence. In addition, NAFLD is sharply elevating worldwide, coincident with the augmented prevalence of obesity. Currently NAFLD has become the major chronic liver disease; NAFLD prevalence in adult population of developed countries is approximately 30% [9]. NAFLD has also become a considerable liver disease in children in response to the elevation of childhood obesity prevalence. Obesity may initiate production of excess ROS and systemic oxidative stress [15] which result in protein and lipid oxidation [16] (Figure 3).



H. Puerto Rican; Hispanic from Puerto Rican origin, H. Dominican; Hispanic from Dominican origin, H. Mexican; Hispanic from Mexican origin.

Figure 3: Influence of Genetic PNPLA3 on NAFLD in USA.

The study from sub-region of USA that compared NAFLD in Hispanic from different origins, showed the greatest NAFLD prevalence in Hispanics from Mexican origin (33%) than those from Caribbean origin (Puerto Rica (18%), Dominic Republic (16%)), ($P<0.01$). The greater NAFLD prevalence remained in Hispanics of Mexicans than Dominican or Puerto Rican origin, even after regulating other factors that discovered to contribute in NAFLD; such as insulin resistance, levels of triglyceride and C-reactive protein, hypertension, serum level of high-density lipoprotein, waist circumference, body mass index (BMI), sex and age [17]. Prevalence of NAFLD might be explained by elevated polymorphism prevalence in the gene encoding patatin-like phospholipase domain-containing 3 (PNPLA3; rs738409 C/G, M148I); especially in Hispanics where it accounts (49%), compared to Non-Hispanics whites (23%) and African-American (17%) [18,19]. Moreover, PNPLA3; rs738409 counts 52% in Hispanics Mexican, 23% in Dominicans [20] (Eric et al., 2019) and 36% in Hispanics Puerto Rican [21]. According to a genome-wide association study [19] elucidated that a non-synonymous sequence variation (rs738409) in PNPLA3 that replaces methionine for isoleucine at residue 148 (I148M) correlates with disproportion in liver lipid profile and the possibility of generating NAFLD. Thus, higher PNPLA3; rs738409 C/G, M148I in Hispanics suggested to take part in fueling NAFLD high prevalence [22] (Figure 4).

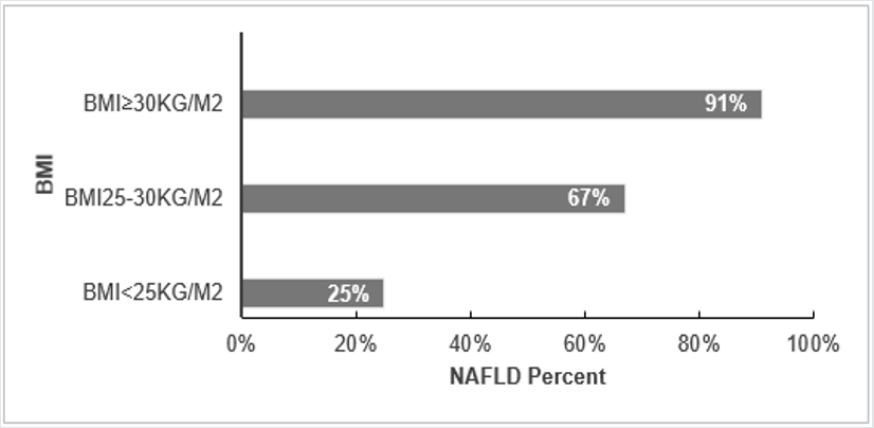


Figure 4: NAFLD Prevalence with BMI in Europe.

BMI correlates with NAFLD, and it has been revealed as a factor that elevates the probability of emerging NAFLD. In years, 1980-2008, the BMI-mean augmented worldwide by 0.4 kg/ m^2 for males and by 0.5 kg/ m^2 for females per decade. This coincides with obesity prevalence that increased simultaneously from 4.8 to 9.8% for men and from 7.9 to 13.8% for Women [23]. This factor

was investigated in the region of European Union and it's clear that similarly to other regions, in Europe the higher risk of acquiring NAFLD is elevated coincidently with the increases of BMI, 25% (BMI<25kg/ m^2), 67% (BMI 25-30 kg/ m^2) and 91% (BMI ≥30 kg/ m^2) [24]. Together with other risk factors (obesity or T2DM) which more likely associate to sedentary life, are increasing in Europe fueling the NALFD prevalence and further the impairments such as cirrhosis and HCC [25].

The NAFLD prevalence among adults of sub- region Shanghai was considered to show high growing trend of NAFLD with time, it's obvious that NAFLD prevalence is elevating with time [26]. The research showed diversity of NAFLD prevalence in different sub-regions of Asian countries, in Taiwan (15%-27%), Korea (24%-40%), and Japan (9%-18%) [27]. Additionally, prevalence in India has increased from 28% in 2015 to 31% in 2016 in the rural region of Haryana [28]. Timely elevation of Fatty Liver was also revealed in different sub-regions of China [29]. Shanghai with high rate in development that goes together with life behavioral changing; the incremental in NAFLD is seen to increase sharply in adults in recent years. Findings supported by [30-33], shown in Figure 5.

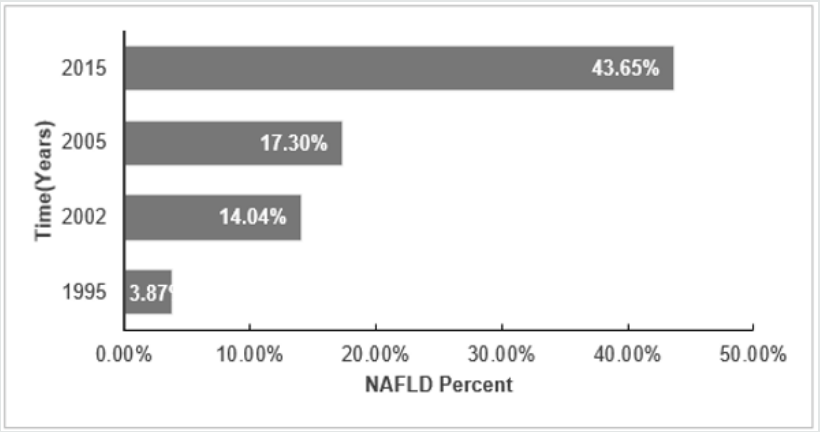


Figure 5: Timely prevalence of NAFLD in shanghai adult.

NAFLD Pathogenesis

Numerous researches have reported that metabolic impairment or disturbance is the basic abnormality in NAFLD [34]. At the center of this discovered metabolic abnormality there is insulin resistance, that also known among the initiators of NAFLD. Thereafter, by provoking oxidative stress, fatty liver may evoke inflammation and hepatocyte injury which may cause the disease to tend to NASH and cirrhosis. The overload of triglycerides (TG) as fat droplets in hepatocytes cytoplasm was reported as the main event of NAFLD, which is a precondition for the succeeding NASH, as it was shown by liver biopsy that 5%-10% of hepatocytes have fat droplets [35]. Increased moving of both TG and free fatty acids (FFA) to the liver, reduced hepatic using of FFA, decrease in export of TG from liver, disturbed beta-oxidation of FFA in hepatocytes result in stockpiling of TG within hepatocytes cytoplasm [34,36,37]. Another main stimulus for liver de novo fatty acid synthesis, is the surplus carbohydrate from either dietary origins or hepatic de novo gluconeogenesis [36,37].

Obesity can be defined as a chronic low-grade inflammatory condition. There are cytokines related to obesity, such as interleukin-6 (IL-6), leptin, adiponectin, and tumor necrosis factor-alpha (TNF-α) that play a remarkable role in NAFLD evolution. Research findings reported that adipose tissue may be the inducer of inflammatory mediators and adipokines, such as pro-inflammatory ones (IL-6, TNF-α, and leptin) and anti-inflammatory (adiponectin) effects [38]. Even though, these hormones and cytokines may ordinally work in balance, the homeostasis is disturbed in NASH that result in increased TNF-α and reduced adiponectin levels. Several mechanisms that likely involve in hepatocellular injury in setting of NAFLD, many of them produce the ROS. A liver with surplus fat can be more prone to stressors, such as adipokines, reactive ROS, and cytokines than normal liver [39,40].

In the study done by Yang and colleagues, obese mice with fatty liver cleared endotoxins less than nonobese controls [38]. Factors that perform key functions in the evolution of NASH from simple steatosis remain unclear [41-43]. Some known possible ways are oxidative stress through increasing ROS and reduced antioxidants, lipid peroxidation, reactive metabolites, 4-hydroxynonenal and malondialdehyde, adipose tissue products. Other discovered ways are Fas-ligand, transforming growth factors-β1, respiratory chain deficiency along with mitochondrial dysfunction, and intestinal microbiota by augmented intestinal permeability, elevated energy gaining from diet, intestinal leak, bacterial lipopolysaccharides (LPS), TNF-α, and endotoxins [44].

Hallmarks in NAFLD

NAFLD and oxidative stress

Oxidative stress increases the loss of structure and function of healthy cells, DNA and also damage of important macromolecules. These conditions are the main roots for chronic diseases such as cancer, stroke, cardiovascular impairment including diabetes [45]. Oxidative stress has been found to disrupt insulin signaling process, which result in insulin resistance in cell [46]. Yet, impaired insulin signaling mechanism remains unclear [47] (Rains &

Jain, 2011). Besides, Elevation of oxidative stress is generally a considerable factor in degenerative diseases, including chronic fatigue neurodegenerative diseases. Moreover, oxidative stress can be suggested to mediates the transition from simple steatosis to steatohepatitis and, disruption of metabolic balance. Furthest, the above cited impairments are the crucial features that lead to steatohepatitis in lipid-laden hepatocytes [48]. Oxidative stress arises due to the lower antioxidant capacity and/or overproduction of the ROS [47]. Various mechanisms by which these two scenarios initiate oxidative stress in organism are described in the following paragraphs.

Several factors initiate oxidative stress in diabetes. The main origin of oxidative stress is mitochondria. Mitochondria use around 98% inhaled oxygen, from which 0.2-2% produce ROS [47,49]. A part of the used oxygen is reduced to water, and the left oxygen converted to oxygen free radicals through oxidative metabolism of mitochondria [50]. Oxygen is required for human life, even though, it may damage and kill the cells when it produces ROS [51]. The ROS are engendered by the reduction of molecular oxygen or from oxidation of water to give products such as superoxide anion, hydroxyl radical, hydrogen peroxide [47]. The hyperglycemia promotes low density lipoprotein (LDL) peroxidation and followed by the production of free radicals [52,53]. The other significant factor in the production of free radicals is glucose oxidation. In its enadiol form, glucose become oxidized in a transition-metal dependent reaction to give enadiol radical anion transformed into reactive radicals [54]. Other mechanism of oxidative stress in diabetes is the engendering of advanced glycated end products (AGEs) [55]. AGEs resulted from the covalent binding of the ketone or aldehyde groups of reducing sugars, in their way to free the amino groups of proteins [47].

Alternatively, Antioxidant may be defined as a substance that delay or inhibit the oxidation of substrate, this scenario comprises many mechanisms pointed out in oxidative stress production pathways. There exist various exogenous and endogenous components which can perform a considerable function in antioxidant defense and help in prevention of oxidative stress in organism including Catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD) [56]. The alteration of endogenous antioxidant defense comes in case of hyperglycemia. In diabetes, both decreases and increases in the activities of major antioxidant enzymes like CAT, SOD, Glutathione reductase (GR), GPx have been noticed [57]. Studies have shown that in pancreatic islets 8-hydroxy-2-deoxyguanosine (8-OH-dG) and 4-hydroxynonenal (4-HNE) levels augmented which support that hyperglycemia might be a key inducer of oxidative stress in the β-cell and oxidative stress induced by glucose [58]. The β-cells of pancreatic islets are vulnerable to the genesis of ROS and the reduction of antioxidant enzymes activities [59]. In Goto-Kakizaki (GK)-rats, the levels of 8-OH-dG and 4-HNE were high in β-cells of pancreatic islets [60]. Many reports have elucidated that the increasing of peroxide content in tissues, plasma, and red blood cells of animals that have chemically induced diabetes [61,62].

NAFLD and Type 2 Diabetes

The apparition of NAFLD exposes to possibility of T2D and in such way exacerbates its complications [63-66]. Multiple factors such as inflammatory adipocytokines and free fatty acids that efficaciously engage in initiation of insulin resistance and NAFLD, are known to be originated from inflamed and inflated visceral adipose tissue [67]. Liver is the prime body organ targeted by accumulation of ectopic fat, and superfluous free fatty acid (FFA) flow into the liver support insulin resistance through initiating NF-kB induction, lysosomal instability, and TNFα activation [68] , cAMP/ PKA pathway [69], or by activation of IL-18 production and NLRP3-mediated IL-1β [70]. The activation of c-Jun N-terminal kinase (JNK) and protein kinase Cε (PKCε) are known to be two ways through which intermediate of liver fat synthesis (Diacylglycerol (DAG)) inhibits signaling of liver insulin [3]. The hepatocytes initiate a redemptive procedure by augmenting mitochondrial β-oxidation to stop FFA, as consequence excess lipid will then hinder capacity of mitochondria antioxidant. Furthest, these will promote insulin resistance that lead to leakage of mitochondria and oxidative stress [71].

Table 1: Various factors expressed in liver steatosis condition that involve advanced complications.

Induced Factor	Changes in Secretion	Promoted Disorder	Sites of Activity Alteration	References
Hepatocyte, fetuin A	Increase	Insulin resistance	Liver, Muscle, Adipose tissue, and pancreas	[90]
PAI-1	Increase	Steatosis, Ballooning, Inflammation, Fibrosis, Vessel damage	Liver, Vessel	[91,92]
Hepatokine, RBP4	Increase	Insulin resistance	Liver, Muscle, Adipose tissue, and pancreas	[93]
ICAM-1	Increase in serum	Systemic inflammation, Lobular inflammation	Liver	[94,95]
Hepatokine, DPP4	Increase	Insulin resistance	Liver, Muscle, Adipose tissue, and pancreas	[96]
TNF	Increase	Intrahepatic inflammation, TG accumulation, Steatosis	Hepatocytes	[68]
Hepatokine, HFREP1	Increase	Insulin resistance	Liver, Muscle, Adipose tissue, and pancreas	[97]

Fibrinogen, factor VII	Increase	Predisposition to CVD	Vessel	[91,98]
P-selectin	Increase in serum	Systemic inflammation	Liver	[94]
Hepatikine, fetuin B	Increase	Insulin resistance	Liver, Muscle, adipose tissue, and pancreas	[99,100]
RAS	Increase	Hypertension, Fibrosis	Vessel	[101]
IL-6	Increase in serum	Systemic inflammation	Liver	[94]
Hepatokine, Selenoprotein P	Increase	Insulin resistance	Liver, Muscle, Adipose tissue, and pancreas	[102]
C-reactive protein CRP	Increase in serum	Systemic inflammation	Liver	[94]

In hepatic insulin resistance, two pathways are proposed to stimulate de novo lipogenesis, either by glucose, via carbohydrate response element-binding protein (ChREBP) [72] or by insulin via sterol regulatory element-binding protein 1c (SREBP-1c) [73]. In addition, insulin resistance obviously known to be induced by the alteration of metabolisms in muscle, liver, pancreas, and adipose tissue that might be initiated from hepatokines. Recently, a number of studies substantiated that secretion of hepatokines with diabetogenic properties become disturbed during liver steatosis condition, See Table 1. Liver steatosis reduces high-density lipoprotein cholesterol (HDL), and increases triglycerides (TG) and low-density lipoprotein cholesterol (LDL). As result, these changes favor the atherogenic dyslipidemia [74]. Likewise, liver steatosis stimulates inflammatory factors and disturbs agents involved in blood coagulation and circulation, which also predispose to CVD risk See Table 1. All these scoped out mechanisms related to NAFLD pathogenesis are proposed to augment the risk of microvascular and macrovascular diabetic complication. Notably, improvement of NAFLD has been revealed to be a manner of modifying probability of generating diabetes [75].

Existing of T2D promote the possibility of NASH generation by two- to three-fold (Portillo-Sanchez et al., 2015). In T2D patient's lipogenesis is high in liver [72,73], accompanying fatty acid oxidation and production of triglyceride. On the other hand, very low-density lipoprotein cholesterol (VLDL) will decrease [76], in this manner, the two incidence NAFLD and T2D often coexist. Primarily, sympathetic fat liver accumulation arises as a defense response to lipotoxicity of free fatty acids that induce metabolic stress [77]. Even though, continual liver free fatty acid influx augment in background, resulting hepatic intracellular triglycerides activate different inflammatory pathways [48]. There are still several outrages in NAFLD patients with T2DM that through different mechanisms initiate the proceeding of NAFLD to NASH, cirrhosis, and HCC [78]. FFA like, ceramides, cholesterol, palmitic acid, and lysophosphatidylchloline; their extra influx in liver of T2D patients, directly lead to lipotoxicity and finally give rise to liver inflammation and fibrosis [79,80]. Metabolism of excess FFAs and oxidation in liver generate oxidative stress [81], which in combination with endoplasmic reticulum (ER) stress [82] lead to hepatocellular injury and apoptosis. Moreover, extra hepatic FFAs, the dissemination of inflammatory mediators (like TNFα, IL-6, and MCP-1) from disordered adipose tissue [80], and endotoxins emanated from gut [83], are obviously mentioned in diabetic patients with NAFLD. As result, these will activate Kupffer cells in liver [84] and release hepatic inflammatory mediators (IL-1β, IL-6, TNFα) that will consequently fuel inflammation and liver damage [85]. The generated hepatocellular damage actuates necrotic and apoptotic hepatocyte death pathways [86], so the continuation of this mechanism finally activates liver stellate cells, deposits of collagen, and liver fibrosis [87]. In another way, with no influence of liver stellate cells activity, liver fibrosis can be generated from insulin resistance by mediating lysyl oxidase-like 2 (Loxl2) [88]. In parallel, oxidative stress, liver inflammation, insulin resistance, ER stress, and hepatocyte death may also induce the regenerative procedure through a lines of growth factors that activate a number of oncogenic signaling pathways, such as JAK/STAT, PI3K/PTEN/Akt, mTOR, NF-kB, NRF-1, and 4HN. And these mechanisms disclosed above contribute to the generation of HCC [89].

NAFLD and Blood Vessels Impairment

Liver is regarded a central organ, that favor its interrelation with various system like cardiovascular and others such as gut, visceral and subcutaneous adipose tissue, and muscle tissues [103]. Circumstances like long-term lipid and glucose metabolism disturbance, oxidative stress, insulin resistance can promote vascular endothelial dysfunction, which is related to endothelial cell damage originated from biological and physical changes including hypoxia and ischemia, hemodynamics, and lipid deposition [104,105]. The lipid overaccumulation and hypercholesterolemia induced by NAFLD can so far, result in endothelial dysfunction subsequent to vascular diseases (VD). Undetermined endothelial function is an early stage in the acquisition of atherosclerosis, ahead of development of plaque inflammation or fatty streaks [106] and hence crucial in CVD development. Postprandial lipid status is consistent with atherogenic form through augmented chylomicron remnants, small quantity of HDL particles and more LDL [107] (Roche and Gibney, 2000). In case of NAFLD patients, the postprandial pathway is hallmarked by enlarged VLDL particles and excess levels of triglyceride-rich [50,108]. Suggested mechanisms through which NAFLD intervene in CVD remain complex and heterogenous. As far as NAFLD obviously known as part of systemic disease and expression of MetS in liver its intercorrelation with CVD could be drawn from the fact that, liver plays an important function in lipid and glucose homeostasis, and hence, is the center of cardiometabolic disease. One of the beginning points is possibly a disparity in calorie-intake and expenditure, overfilling the adipose tissue capacity of storage resulting to the buildup of ectopic fat, involving hepatic fat [42]. Liver enzymes elevation are correlated to stroke [109]. NAFLD Patients expose endothelial malfunction

of conducting vessels, along with microvasculature [110]. Arterial stiffness known as a well-recognized marker of CVD anteceding arterial hypertension, and NAFLD remain independently allied to rising of vascular stiffness [110]. Discrepancy of living condition, glycaemic control and body weight may substantially influence disease progression.

A make for the effective carotid plaque burden/generalized atherosclerotic burden known as carotid intimal media thickness (cIMT) interplays with NAFLD [111]. In case of cirrhosis, intrahepatic and mesenterial endothelial irregularity are encountered [112]. Same as in NAFLD, intrahepatic dysfunction appeared [113] yet, interestingly, no inflammation or fibrosis reported [114,115]. So, this is implicated as an early phenomenon that proposed to lead to disease progression. Even though is more pronounced in NASH, Endothelial dysfunction of systemic circulation has been also found in NAFLD [116]. An endogenous antagonist of nitric oxide synthase (NOS) known as Asymmetric dimethyl arginine (ADMA) was discovered to be positively allied to CVD. Reduced breakdown, in which liver perform a vital function [117], is suggested to result in elevated ADMA levels [77]. Moreover, NAFLD patients show elevated quantity of circulating ADMA, a coalition ceasing after the reparation for metabolic risk factors [117]. Other numerous markers involved in endothelial dysfunction (like, endocan) have been also found to elevate in NAFLD [118] \. An undisturbed endothelial monolayer is fundamental for normal vessel wall performing. Ruination of this layer performs a role in atherogenesis, that is marked by endothelial microparticles (EMPs) elevation, showing disruption of endothelial. Apart, the endothelial progenitor cells (EPCs), reported to indicate endothelial repairmen, their circulating levels decreased, and their adhesive activity also weakened in NAFLD [119].

Liver microvasculature manifest a remarkable modification in NAFLD condition, these are: deformation of the sinusoidal pattern, sinusoids compress by fat-burdened hepatocytes and fenestrae ruination [120]. And these distortions appear due to the generation of fibrosis and inflammation as a sign of preliminary phenomenon [114]. These disproportions in structure are known to take part in accelerating portal pressure observed in non-cirrhotic NAFLD, in humans and animals [114]. In arterial stiffness condition that increases relating to NAFLD and CVD, there is alteration in structure of 'media' in large arteries: its crosslinking and collagen content increases, contrarily elastin fibres decrease, so as to get fractioned [121]. Quantities of metalloproteinases, same as serum elastase are connected with arterial stiffness [121]. Interestingly, in NAFLD this arterial stiffness was found to be elevated [122], others made a proposition of a potential activity of TGF-β [123]. The role of preventing the formation of atherosclerosis done by laminar flow on vascular endothelium known to be induced by Nrf2 activation (Kim et al. 2012). Furthest, Nrf2 has been yet reported to extenuate neointimal hyperplasia originated from vascular injury [124].

Non-Coding Rnas Improve NAFLD

Non-Coding RNAs (ncRNAs) is a set of molecules that is regularly incorporated in NAFLD pathogenesis. ncRNAs typically shows high cellular or tissue specificity, allowing them great potential for predicting disease progression. In case of NAFLD as well as in other diseases ncRNAs may have a critical role as appropriate biomarkers and good indicators in assessing the severity of disease [125]. Most examined non-coding RNAs are miRNAs. Times ago, panels encompassing several serum miRNAs and other biochemical indicators, unveiled miRNAs to have high diagnostic indices for NAFLD and a higher predicted NASH potential compared to biomarkers [126,127]. In addition, miRNAs have been discovered to intervene in lipid metabolism, inflammation, insulin resistance, fibrosis, as well as HCC generation. Knowing their correlation with severity of disease, miRNAs can be biomarkers used in early noninvasive diagnosis and evaluation of NAFLD severity. Sensitive biomarker for early detection is accessed through assessing miRNAs serum levels [125]. Therefore, some critical points and pathways are scoped out in the following paragraphs.

First point investigates the role of miR-155, this has shown the ability to regulate some proteins and cytokines obviously known to participate in NAFLD progression, as cleared in following discussion. The Cytokines TNFα, IL-6 have been suggested to perform a greater role in NAFLD pathogenesis [128], as their elevation and secretion have been discovered to be increasing in serum of NASH patient (Kassel et al., 2010). Again, Park et al. unveiled that pro-inflammatory cytokines IL-6 and TNFα are crucial for the progression from steatosis to steatohepatitis in obese mice, and that absence of IL-6 or TNFR1(receptor that bind TNFα) decreased lipid accumulation in liver, as well as reduction of macrophages and neutrophils influx in high fat fed diet mice [129]. Beyond this, in their absence, levels of reactive oxygen were also lowered, together with the AKT, mTOR and COX2 proteins. The findings of Qu et al. have reported similar suppression of IL-6 and IL-1b in response to miR-155 or miR-21 inhibitors, showing that these inflammatory factors are regulated positively by miR-21 or miR-155. In addition, obesity and NAFLD in another way can develop in response to elevated white adipose tissue mass corresponding to miR-155 deficiency/downregulation. Furthest, hepatic steatosis augmented in miR-155 mice fed with HFD for 6 months [130].

Second point investigates the role of miR-22, for its elucidated potentiality in revealing different degrees of liver abnormalities in NAFLD, as cleared in this paragraph. The research findings revealed that the serum level of miR-122 in mice with a methionine-choline deficiency (MCD) diet has augmented 40-fold, overstepping serum alanine aminotransferase (ALT) (4.8-fold) and aspartate aminotransferase (AST) (3.3-fold) [131]. Additionally, it was explicated that increased levels of serum miR-122 occurred in NAFLD rats even without elevated ALT augmentation [132]. Hence, the sensitivity of miR-122 is better than the one of cytokeratin (CK)-18, ALT, or AST while detecting NASH and predicting liver fibrosis in patients with NAFLD [133].

Another complication that commonly involve in pathogenesis of several diseases is the abnormal cell proliferation. So, the inhibition of this pathological process has been clarified as critical way in treating precited disease [134], through targeting miRNA, lncRNA, or ceRNA crosstalk. In case of elevated quantity of PPARα, its target gene carnitine palmitoyltransferase 2 (CPT2) and the acyl-CoA

binding domain containing 3 (ACBD3) or the solute carrier family 27A (SLC27A) become activated, and the steatosis is lowered [134]. Therefore, scircRNA/miR-34a/PPARα Pathway is suggested to be incorporated in progression of NAFLD. Moreover, the critical role of noncoding RNAs in NAFLD was investigated in a number of studies which explained that both circRNA 0046367 and circRNA 0046366 the endogenous regulators of miR-34a [134, 135] block miRNA/mRNA cooperation with miRNA response element (MRE) and lastly can extinct inhibitory effect on PPARα. These enabled to propose that dysregulation mechanism of circRNA 0046366 or circRNA 0046366/miR-34a/PPARα signaling pathway may be a novel mechanism that lead to hepatic steatosis [134].

Conclusion

NAFLD is etiologically correlated with systemic distortion of various metabolisms, of which their impairment result in multiple disorders such as: insulin resistance, hyperglycemia, hyperlipidemia and other complications correlated with obesity and diabetes. Insulin resistance is illustrated like a central root that likely initiates the coexistence of diabetes and NAFLD. Moreover, mitochondria hyperactivity and shortage in antioxidants initiate liver oxidative stress. That induce inflammation which aggravate the liver cell damage by accelerating the progression from simple steatosis to NASH, that progress to other irreversible forms of NAFLD. Besides, cytokines related to obesity, such as interleukin-6 (IL-6), leptin, adiponectin, and tumor necrosis factor-alpha (TNF-α) work in harmony, but their homeostasis is disturbed in NASH, that also worsen NAFLD. The prevalence of NAFLD elevated the risks of acquiring other diseases either related to Insulin resistance, as co-inducer (such as Type 2 diabetes) or from subsequent damages (such as cardiovascular diseases, from vessels damage). The management of NAFLD rely on early detection and severity quantification, the noncoding RNAs have shown these abilities with high sensitivity. Obesity and NAFLD can also develop in response to elevated white adipose tissue mass, derived from miR-155 deficiency/downregulation. These facts allow us to suggest also that noncoding gene can play role in handling the disease. Moreover, also many other different mechanisms involved in developing NAFLD, and interconnecting pathways with other metabolism complications (such as diabetes, obesity and cardiovascular diseases) are encompassed in this study. However, currently no specific medication for NAFLD, future researches can base on advancing analysis that amalgamate findings on NAFLD in its complexity and its interrelation, like current study, to further in management of NAFLD and in case diverse disorders involved to aggravate condition.

Acknowledgement

This study was supported by National Natural Science Foundation of China (30725045).

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DOI: 10.32474/CTGH.2020.03.000151