Current Aspects of Hepatic Lipotoxicity in Metabolic Associated Fatty Liver Disease

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Abstract: Metabolic associated fatty liver disease (MAFLD) is an increasing health problem affecting 20 to 30% of the global population, due to its strong association with obesity and type 2 diabetes mellitus (T2DM). Metabolic steatohepatitis and its progression to cirrhosis is the second cause of chronic liver disease in the world. Hence, early identification of this inflammatory state and understanding of the pathogenesis, will help to focus and treat an early state of this disease. Several factors contribute to the inflammation of the liver and the development of steatohepatitis among them insulin resistance, oxidative stress, lipotoxicity and bile acid toxicity. Adipose tissue (AT) and lipotoxicity plays a key role in the development and persistence of inflammation in MAFLD, by the alterations of the balance of adipokines in an insulin resistant AT, the secretion and activation of pro-inflammatory pathways, the mitochondrial and endoplasmic reticulum dysfunction and the consequent oxidative stress, as well as the secretion of free oxygen reactive species. A good understanding of the hepatic lipotoxicity and the role of the AT will help us to work out for the development of new strategies for treating this disease.

Keywords: Metabolic associated fatty liver disease, Metabolic steatohepatitis, Liver fibrosis, Adipose tissue, Hepatic Lipotoxicity.

1. INTRODUCTION

Non Alcoholic Fatty liver disease (NAFLD), recently renamed, as Metabolic Associated Fatty Liver disease (MAFLD) due to its association to metabolic dysfunction [1,2] is an increasing health problem, being the primary liver disease in Western countries that affects 25% of the worldwide population. This change of name might help patients understand the etiology of the disease [1-8].

This disease is one of the most prevalent causes of chronic liver disease [9,10], and is directly associated with the increasing prevalence of type 2 diabetes mellitus (T2DM), metabolic syndrome and obesity [10,11]. Other risks factors for MAFLD are waist circumference, hyperinsulinemia, hypertriglyceridemia and impaired glucose tolerance [10,12]. Dyslipidemia has been associated with MAFLD and an increased risk of advanced fibrosis or cirrhosis [12]. Another preoccupying fact is the increase incidence of obesity in children; in 2010, 16.9% of the children were obese, that will increase the susceptibility to developing MAFLD in adulthood, as well as the risk of liver related complications and hepatocellular carcinoma [13].

MAFLD has a spectrum ranging from simple steatosis to the inflammatory state known as metabolic steatohepatitis [14], the latter could progress to cirrhosis, which is a worldwide health problem causing a mortality rate of 25.56 per 1000 person-years [15]. Carrying an important economic burden and an increased risk of liver related death and of cardiovascular diseases [15-17].

Several factors, including lipotoxicity, insulin resistance, inflammation, oxidative stress, and bile acid (BA) toxicity, have been associated with metabolic steatohepatitis progression. Hepatic lipotoxicity has been described to be part of the pathogenesis of metabolic steatohepatitis, due to the overwhelmed capacity of the liver to metabolize and export free fatty acids (FFAs), as triglycerides (TGs); the main mechanisms responsible for this lipotoxicity are the mitochondrial and ER oxidative stress and bile acid toxicity [17]. Another factor recently describe associated with hepatic lipotoxicity is the CD36 fatty acid translocase contributing to MAFLD progression, being the FFAs inimical agents to the hepatocytes [18].

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Hepatocytes senescence might be another related factor associated to metabolic steatohepatitis progression [19].

The present review focuses the new concepts of the molecular mechanisms of lipid-induced hepatocellular damage.

2. THE ROLE OF ADIPOSE TISSUE

Adipose tissue (AT) is a basic site for lipid storage, energy homeostasis and insulin sensitivity [20]. Adipose tissue has been classified by its function as white and brown; and by its location in subcutaneous and intra-abdominal. The white adipose tissue is an important site for energy homeostasis, endocrine activity and insulin sensitivity; while brown adipose tissue main function is thermogenesis. Besides, the intrabdominal fat has been divided into visceral and retroperitoneal. The visceral adiposity is closely related to MAFLD and is associated with systemic inflammation. The adipose tissue is constituted by different kind of cells among which are endothelial cells, fibroblasts, pre-adipocytes, macrophages and immune cells beneath others [20,21]. The proper functioning of the adipocytes depends on several factors including their number, size, hormonal effects and their communications to other cells [21]. The adipocytes maturation is closely linked to several transcription factors as peroxisome proliferator-activated receptor gamma (PPRA-γ), sterol-regulatory element binding protein (SREBP-1), CCAAT/enhancer-binding proteins (C/EBPs), signal transducers and activators of transcription (STATs), and Kruppel-like factor (KLF) proteins; among others, giving them the capability to adapt to overfeeding [20,22].

Also, there have been studied other transcription factors engaged on adipogenesis, as members of the activating protein 1 (AP-1) (v-Jun, c-Jun, JunB, JunD, v-Fos, c-Fos, FosB, Fra1, Fra2), KLFs (KLF 4,5,6 and 15), C/EBPs, SREBP-1 (SREBP: SREBP-1a, SREBP-1c, and SREBP-2. SREBP-1a and SREBP-1c), STATs, [20], EBF1 (164343), KLF4 (602,253), KLF5 (602903), KLF6 (602053), KLF15 (606465), EGR2 (129010), CEBPA (116897), CEBPB, CEBPG (138972), SREBP1 (184956), ARNTL (602550), on the other hand, there have been reported transcription factors that downregulate adipogenesis as, Wnt, GATA factors (GATA2 (164343), GATA3 (131320)), KLF (KLF2 (602016), KLF3 (609392)), Pref-1, IRF3 (603734), and IRF4 (601900) [20,23].

The mature adipocytes have the potential to adjust to the increase need of fat storage becoming hypertrophic (increased adipocyte size) and hyperplasic (increased number of adipocytes), and these hypertrophic adipocytes produce adipokines, some of which like resistin contributes to inflammation and insulin resistance [24].

Both type of adipocytes metabolize lipid in a different way, white adipocytes storage triglycerides and release them by lipolysis during fasting; while brown adipocytes oxidize them to produce heat [20].

The adipose tissue lipid accumulation and release depends on the balance between lipogenesis and lipolysis [25].

Lipolysis takes place in the adipose tissue while lipogenesis can occur in the liver as well as in the adipose tissue. Lipolysis is due to hormonal and biochemical signals that stimulates the hydrolysis of triacylglycerol and results in the liberation of glycerol and FFAs to the circulation from the white adipose tissue. Increased lipolysis may occur in the context of fasting, catecholamine release, glucagon, but also an increased lipolysis occurs in insulin resistance and obesity, which are the main factors associated with MAFLD. Surprisingly insulin is the main anti-lipolytic hormone, nevertheless, the impaired sensitivity of the adipocytes to insulin may contribute to the enhanced lipolysis in these conditions [26].

There has been recently described the association of MAFLD genes expression, insulin resistance and de novo lipogenesis; among these genes are APOB, DEGs-, FABP4, FABP5L2, CD24, SPP1, PRAP1, MTP and L-FABP. The increased expression of these genes results in the increased hepatic fat influx and deposition, resulting in lipotoxicity, oxidative stress, cell adhesion and migrations as well as fibrosis. Their interaction between FABPs and CD36 increases the intrahepatic lipid accumulation and insulin resistance [27].

Several transport proteins are implicated in FFAs uptake among them the plasma membrane fatty acid binding protein (FABPpm), caveolin 1, Fatty acid Transport proteins (FATPs), and the CD36 translocase. The CD36 translocase acts as a receptor of LDL and receptor and transporter of FFAs, it facilitates intracellular FFAs uptake and esterification of FFAs to triglycerides; its overexpression drive to an increased influx of FFAs in the liver. Interestingly, CD36

translocase not only regulates FFAs uptake and esterification but also oxidation, lipid synthesis, VLDL secretion, inflammation and autophagy. The expression of this translocase in the liver is initially low but it is importantly induced by the lipid overload, so its expression increases gradually with hepatic TGs overload. Consequently, the overexpression of CD36 translocase drives to an increase FFAs uptake and a reduced FFAs Beta-oxidation [28].

Also, it has been described that this adipose tissue dysfunction leads to secretion of pro-inflammatory cytokines and the alteration of the production of adipokines that control insulin resistance and satiety like adiponectin and leptin.

3. HEPATOCELLULAR LIPID METABOLISM AND THE LIPIDIC HEPATIC ACCUMULATION

The liver and the AT are the main sites for the synthesis and metabolism of FFAs. In the lipid metabolism, the liver has three important functions: degradation of the FFAs to small compounds to give energy to the body; synthesis of other lipids from FFAs as phospholipids and cholesterol, and synthesis of triglycerides from carbohydrates and some proteins. In the liver, glucose transforms to acetyl-CoA and by the enzyme acetyl-CoA carboxylase through its association with manolyl-CoA it converts in to Palmitic-acid; which in its turn produce Pamitoyl-CoA and Stearoyl-CoA that further on, and by the action of the enzyme diacylglycerol O-Acyltransferase 2 (DGAT2) forms triacylglycerol. In the other hand, Acetyl-CoA may convert to HMG-CoA for the cholesterol synthesis, and by the action of the HMG-CoA reductase produce mevalonate [29].

It has been recently described, that the inhibition of the acetyl-CoA carboxylase (ACC) reduces fat accumulation, hepatic de novo lipogenesis as well as the hepatic lipotoxicity; also might alter the profibrogenic activity of the stellate cells (HSCs) [30].

There are genes, ACLY, FASN and SCD1 among others, involved in the synthesis of FFAs in the liver. The transcription of these genes is regulated by several transcription factors one of which is the sterol regulatory element-binding protein 1c (SREBP-1c), whose activity is regulated by factors and signaling pathways such as PI3K/Akt and mammalian target of rapamycin (mTOR) complex 1 (mTORC1) [31].

The first important fact for the development of MAFLD is the intrahepatic triglycerides accumulation, coming from the diet or originated from the hepatic esterification of FFAs and glycerols, due to lipolysis in the white adipose tissue and to the de-novo lipogenesis. This accumulation mainly due to the overwhelmed capacity of the liver to metabolize and export triglycerides to peripheral tissues leads to mitochondrial dysfunction and ER oxidative stress, promoting the activation of inflammatory pathways, and cell death [32].

As described above, lipotoxicity cause hepatocellular death due to mitochondrial injury, ER stress and the activation of c-Jun-N-terminal kinase (JNK), as well as, the release of damage-associated molecular patterns (DAMPs) by the hepatocytes, that stimulates innate immune system by binding to toll liker receptors (TLR), such as TLR4; and NOD like protein 3 (NLRP3) inflammasone which stimulate a pro-inflammatory secretion of cytokines and chemokines. [33-35] This ER also stimulates the NFkB pathway leading to a dysregulated unfolded protein response (UPR) developing apoptosis and liver injury [36].

4. LIPOTOXICITY

Lipotoxicity plays a crucial role in the pathogenesis of MAFLD. Lipotoxicity is distinguished by an increased concentration of toxic lipids and lipids derivatives. Among lipids that causes lipotoxicity are FFAs, TGs, lysophospatidil cholines (LPCs), free cholesterol, ceramides and bile acids. There has also been described lipids that protect the liver against lipotoxicity damage among them omega 3, 6, the recently described omega 5 and perplin 5.

It has also been described the role of micro-RNA in lipotoxicity, the hepatocyte-derived exosomal miR-192-5p has an important role in the activation of macrophages and the trigger of the proinflammatory cascade through a Rictor/Akt/FoxO1 [37].

Among other miRNA that have been described to have a role in lipotoxicity in metabolic steatohepatitis feature the miR-29, miR21, MiR-33, miR34a, miR-103/107, miR122, miR181a, miR-221/222, miR 375, miR-802. In this miRNA, miR29a has been found to modulate via miR-29a/CD36/mitochondria axis promoting mitochondrial damage and the expression of oxidative stress and reactive oxygen species, as well as promoting lipid accumulation and peroxidation where the activation of NFkB and further on activation of kupffer cells promotes the proinflammatory cascade [38].

There has additionally been described miRNA that have a protective effect against lipotoxicity and hepatic steatosis among them miR-22 by the signaling pathway of p53/miR-22/SIRT17PPARα [39].

4.1. Toxic Lipids

Several lipids have been described for their role in lipotoxicity activating inflammatory pathways.

Free Fatty acids (FFAs) are important mediators of hepatic lipotoxicity, by inducing hepatic steatosis and as acting as cellular toxins. FFAS may cause lysosomal permeabilization with Bax translocation causing cathepsin B release in to the cytosol activating NFκB with TNFα generation. Bax proteins are cytosolic proteins that induced channel formation causing organelle permeabilization. FFAs stimulates TNFα expression in a NFκB dependent pathway. TNFα is an important mediator of persistence of insulin resistance (by signaling IKK-β activation and c-Jun-N terminal kinase activation), promotes lipid accumulation and hepatic steatosis [36,40]. The accumulation of free fatty acids in the liver also increases endoplasmic reticulum stress, in a lipid load dependent way, activating pathways associated with lipid stress. Hepatic steatosis is a stressful condition limiting the ability of the liver to deal with additional stress o damage; regenerative capacities of steatosic liver is reduced [41].

Lysophosphatidylocholine (LPC) is a biologically active lipid that is considered an important mediator of hepatic lipotoxicity, originated by the activity of lecithin-cholesterol acyltransferase (LCAT), this lipid seems to be involved in the pathogenesis of MAFLD and its transition to metabolic steatohepatitis. It has been found, to downregulate genes involved in fatty acid oxidation and metabolism; as well as to upregulate genes shrouded in cholesterol biosynthesis. Also it has been described that LPC triggers hepatocellular apoptosis through alteration of the mitochondrial integrity, in addition to enhancing the secretion of proinflammatory and profibrogenic molecules [42].

Sphingolipids have also been described to be involved in MAFLD, beneath them the ceramides, the most importantly linked to lipotoxicity. The liver the main site of synthesis of this lipids by different pathways: de novo synthesis, the main pathway of production, by the reaction with the serine palmitoyl-CoA transferase (SPT) stimulated by a rich saturated fat diet, that increases the influx of FFAs with the consecutive inflammation and oxidative stress that increases the activity of the SPT, the sphingomyelinase pathway by the hydrolysis of sphingomyelin and the salvage pathway by the degradation of complex sphingolipids into sphingosine by a ceramidase activity [43-45]. Ceramides have shown to alter insulin signaling and sensitivity. It has also been described the deleterious effect of ceramides in mitochondrial respiratory activity as well as in membrane biophysical properties, impairing mitochondrial function, generating reactive oxygen species and reducing the acylcarnitine production [44].

Sphingolipids have also been associated with obesity, and it has been recently described that the depletion of adipocyte sphingosine kinase 1 that generated S1p increases the inflammation in the liver and in the adipose tissue [45].

The intestinal microbiota plays a crucial role in MAFLD. Gut microbiota regulates bile acid metabolism pool size, hydrophobicity and enterohepatic circulation [46]. In MAFLD, it has been describe an alteration in gut microbiota, this dysbiosis alters the conversion of primary bile acids into secondary; leading to a reduction of the synthesis of secondary bile acids which decreases the activation of several nuclear receptors among them the farnesoid X receptor (FXR), the pregnane X receptor and the vitamin D receptor; which are thought to be important in energy regulation as well as in hepatic ceramide synthesis [47,48]. A recent study reports that the activation of intestinal FXR stimulates the synthesis of ceramides, the increase in ceramide production and reduction in its clearance (by the decline of adiponectin) leads to hepatic accumulation and ER stress and production of ROS in the mitochondria [49].

4.2. Protective Lipids and other Regulatory Protective Molecules

There have been described lipids that protect against steatosis and against apoptosis. Among them there have been described the protective effect of fatty acid omega 3 and omega 6. Omega 3 has shown to reduce visceral fat and decrease adipocytes hypertrophy [49,50].

In other studies omega 3 fatty acid have shown to neutralize the palmitate induced lipid accumulation, therefore mitigate lipotoxicity, maintaining mitochondrial integrity; [51] and reducing mitochondrial oxidative stress, ameliorating palmitic acid induced lipid toxicity [52].

Recently it has been published the effect of other omega fatty acid, the punicica granatum acid (omega 5) as an hepatic protector of lipotoxicity, that increases fatty acid oxidation within the hepatocytes, enhancing the antioxidant gene expression and reducing systemic oxidative stress [53].

It has also been described the effect of fish oil and chicoric Acid (CA) in the upregulation of AMPK-mediated PPRAα/UCP2 and the downregulation of AMPK-mediated SREBP-1/FAS signaling pathways, suggesting their protective effect in MAFLD and lipotoxicity [54].

A recently published study described the protective effects of a lipid protein called Perilipin 5 (PLIN5) that is highly expressed in oxidative tissues including the liver and that is thought to have a role in protecting the liver against lipotoxicity; mitigating the ER stress and the proinflammatory signaling [55].

Another protective molecule involved in lipotoxicity is the six span transmembrane protein embedded in the endoplasmic reticulum, member of the insulin-induced gene family, insulin-induced gene 1 (Insig-1), has shown to be engaged in the balance of intracellular lipid metabolism homeostasis by heading the activation of sterol regulatory element-binding proteins (SREBPs) and the degradation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR). Recent data has shown that Insig-1 lower lipid accumulation in hepatocytes, suppresses adipogenesis and inhibits the differentiation of adipocytes [56].

5. SENESCENCE OF HEPATOCYTES

It has been recently reported that senescence might play a role in metabolic steatohepatitis, by the upregulation of miR34a that induces hepatocyte senescence, by targeting the upregulation of the cyclin-dependent kinase inhibitor 1 (CDKN1 or p21) and the downregulation of cyclin-dependent kinase 6 (CK6) signaling pathway [57].

6. CLINICAL IMPLICATIONS OF LIPOTOXICITY

Metabolic steatohepatitis is the progressive inflammatory form of MAFLD. The mechanisms involved in this inflammatory state are wide, including lipotoxicity, hepatic injury and apoptosis, and consequent fibrosis. Lipotoxic mediators that trigger hepatic and systemic inflammation includes: ceramides, FFAs, triglycerides, lysophosphatidyl-choline and free cholesterol, the overwhelmed capacity of the liver to metabolize FFAs by the mitochondrial fatty acids oxidation leads to oxidative stress and mitochondrial dysfunction, as well as an ER stress. The insulin resistant adipose tissue secrete proinflammatory mediators as wells as “bad” adipokines as resistin; and reduce the secretion of “good” adipokines as adiponectin and leptin. This entire inflammatory environment leads to continues lipotoxicity and systemic inflammation and oxidative stress. In the liver, this mitochondrial injury and oxidative stress leads to the activation of c-Jun N- terminal Kinase (JNK) and the release of damage associated molecular patterns (DAMPs) that stimulates the innate immunity and induces the secretion of proinflammatory chemokines and cytokines; with the activation of macrophages and stellate cells; and activate proapoptotic signaling pathways leading to hepatocellular death (Figure **1**) [17,36,37,58].

7. TREATMENTS THAT TARGET LIPOTOXICITY

7.1. Dietary Interventions

7.1.1. Coffee

Several antioxidant properties have been attributed to the consumption of coffee; it has been shown that coffee consumption has a dose-dependent beneficial effect on the risk of developing MAFLD, reducing fat deposition and metabolic derangement through regulation of the fatty acid oxidation, energy metabolism, and cholesterol efflux [59]. Coffee consumption has also shown a beneficial effect in the liver fibrosis progression in MAFLD patients [60]; compared to those patients who didn’t drink coffee with a RR of 0.68 (95% CI 0.68-0.79) [61] Coffee consumption might have a role also in the gut microbiota, showing in a clinical trial that 12 weeks of caffeine increases the gut Bifidobacteria [62].

7.1.2. Polyunsaturated Omega Fatty Acids

Omega 3 has a role in improving the levels of triglycerides, total cholesterol, and HDL, and might have a role reducing hepatic lipid deposition; [63] nevertheless; their effect in reducing hepatic inflammation has not been proved. It has also been discuss that the dysbiosis present in patients with MAFLD may modify the absorption, bioavailability of ingested omega 3 and 6 [64]. It has also been published the effect of omega 3 in reducing LPS serum levels [65]. Recently, in a mice MAFLD model, it has been shown that punica granatum (omega-5) improves hepatic steatosis, as well as insulin resistance, energy expenditure and oxidative stress [53].

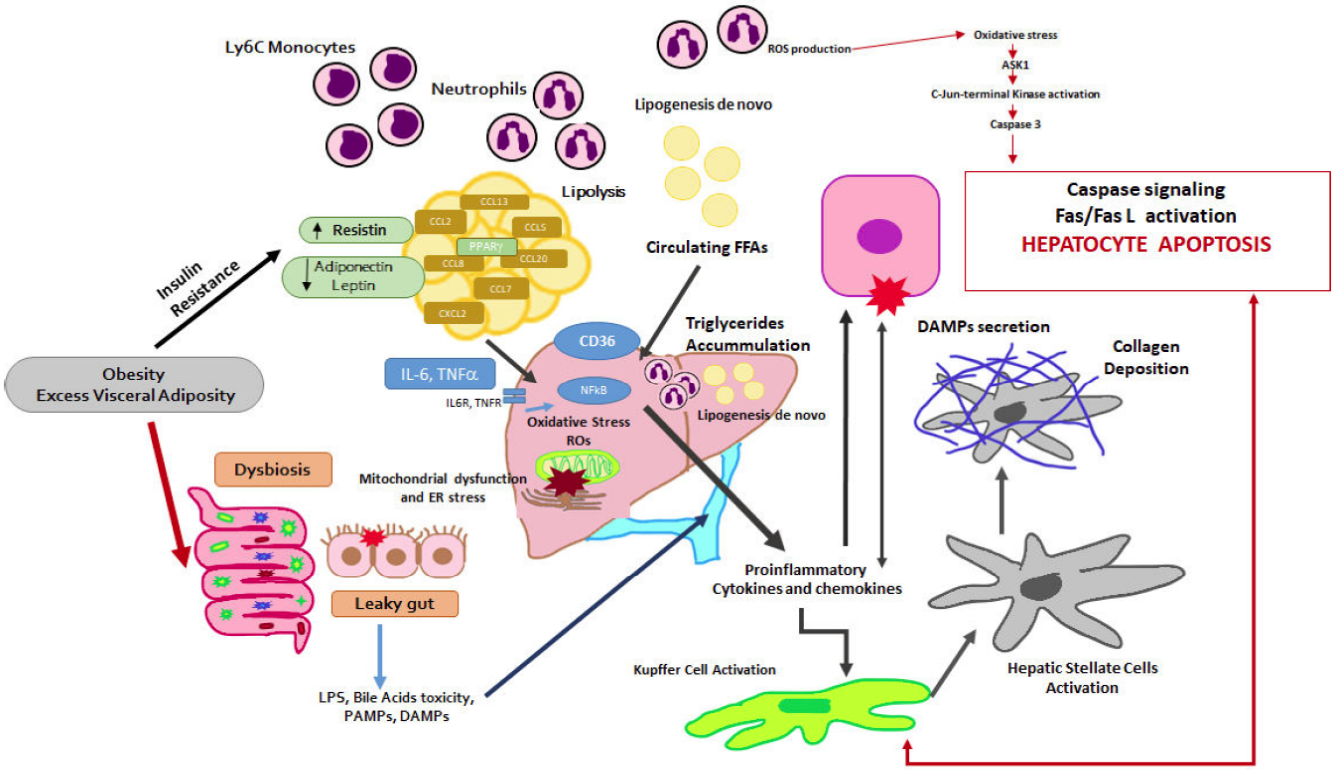

Figure 1: Main aspects of hepatic lipotoxicity. Obesity and Excess of Visceral Adiposity leads to 1) insulin resistance, that alters the relation of adipokines in the insulin resistant adipose tissue contributing to the activation of PPARγ, as well as the secretion of pro-inflammatory chemokines and cytokines. Lipolysis and lipogenesis de novo cause the accumulation of Free Fatty acids (FFAs) within the liver, the overwhelmed capacity of the liver to metabolize excessive intrahepatic lipids result in mitochondrial and ER dysfunction leading to a oxidative stress that activated ASK-1 and c-Jun Kinase, triggering caspase signaling with consecutive hepatocellular death. 2) Dysbiosis and "leaky gut" causing the transportation of LPS, PAMPs and DAMPs within the portal tract to the liver perpetuating this pro-inflammatory cytokines and chemokines secretion, with the consequent kupffer and Stellate Cells Activation, leading to hepatic fibrosis (modified of the reference [17]).

7.1.3. Target to Gut Microbiota

Gut microbiota might contribute to the development and progression of MAFLD; actually, patients with MAFLD have been shown to have dysbiosis [65-67].

In this sense, there has been evaluated the effect of the administration of an hyper immune bovine-colostrum (IMM 124-E) in patients with MAFLD, they observed that its administration was safe, with no side effects; it has been shown a decrease in fasting glucose levels, improve in glucose tolerance and lipid profile; as well as an increase in protective adipokines as adiponectin; a raise in T regulatory cells and in the levels of glucagon-like peptide 1 (GLP-1) [68].

Antibiotics effect on metabolic steatohepatitis has also been evaluated; among them Cidomycin and Rifaximin both have shown a reduction in transaminases levels, circulating endotoxins and proinflammatory cytokines; showing the importance of dysbiosis in systemic inflammation in Metabolic steatohepatitis. Antibiotics might have a beneficial effect promoting the "good" bacteria to grow; nevertheless, long-term use of antibiotics in MAFLD patients should be cautiously evaluated [65,69,70].

Pro, syn and prebiotics have also been tested, they might have a beneficial effect ameliorating the gut microbiota and improving the function of the intestinal barrier; enhancing the expression of tight junction proteins; among the probiotics that have been tested are Lactobacillus casei DN-114001, VSL#3, Lactobacillus plantarum MB452, beneath others [71-73].

7.2. Pharmacological Interventions

7.2.1. Vitamin E

Current guidelines for treatment of patients with MAFLD includes the treatment with vitamin E 800UI/day, which improves liver histology in patients with biopsy proven MAFLD; nevertheless, there has been described an increased in all-cause mortality, the risk of prostate cancer and hemorrhagic stroke so risks and benefits should be evaluated with each patients

[74,75]. The mechanism of action of vitamin E in MAFLD might be in lipid peroxidation as well as in reducing ROS generation, reducing oxidative stress [76]. It has also been described that vitamin E reduces inflammation and metabolic profile in patients with obesity [77].

7.2.2. Pioglitazone

A thiazolidinedione drug class that target the PPARγ. It has shown to ameliorate liver histology in patients with MAFLD at the dose of 45mg/day in diabetic and non-diabetic patients; however, risks and benefits should be evaluated in each patients before its prescription [74,75]. the mechanism of action of this drug as a PPARγ agonist suppress insulin resistance, protects against ER stress and inflammation [78]. It has also been described to have a protective effect reducing lipotoxicity by the inhibition of the activation of the TLR4 signaling pathway [79].

7.2.3. FXR Agonists

FXR activation reduce the bile acids synthesis and promotes their conjugation, protecting the liver from the deleterious effect of excessive bile acids accumulation. Nevertheless, Ursodesoxicolic Acid (UDCA) in large clinical trials has shown not effect histological improvement in patients with NASH [80,81]. Obeticolic Acid (OCA) has also been tested for MAFLD in REGENERATE trial, OCA improved liver fibrosis in patients with MAFLD; nevertheless, it cause an augmentation of LDL which might traduce in a proaterogenic effect, the other important side effect is pruritus [82]. FLINT trial showed the same histological improvement in patients with non-cirrhotic MAFLD but long term safety is still a concern [83]. Other FXR agonists that are been evaluated for the treatment of MAFLD are Tropifexor, EYP001a, Cilofexor and Px-104; there are been evaluated other molecules that act in bile acid absorption among them Colesevelam, Colestimide and Volixibat [69].

7.2.4. Glucagon Type Peptide 1 Analogue

Liraglutide have shown to decrease lipotoxicity by inactivating the mammalian target of rapamycin (mTOR) signaling molecules, being this pathway importantly involved in high lipid level-induced inflammation. Importantly, liraglutide may protect against lipotoxicity-induced inflammation by regulating mTORC1-dependent pathways [84].

7.2.5.Dipeptidyl Dipetidaase-4 (DPP-4)

Inhibitors seems to have little or no effect in MAFLD and hepatic lipotoxicity, [85] nevertheless, sitagliptin has shown, in combination with metformin, to reduce body weight, intrahepatic lipid and visceral adipose tissue, and to improve glycemic control in diabetic patients with MAFLD [86].

7.2.6.Sodium-Glucose Cotransporter (SGLT-2)

Inhibitors also appear to reverse metabolic abnormalities [85]. Empaglifozin (EMPA) and dapaglifozin (DAPA) seems to mitigate lipotoxic damage in angiogenic cells [87]. Ipraglifozin has been described to improve ER stress and to reduce apoptosis as well as lipid deposition; [88] also it has been published its effect in reducing insulin resistance and lipotoxicity in metabolic steatohepatitis models [89].

8. CONCLUSION

Lipotoxicity is an important mechanism of hepatocellular damage in patients with MAFLD, which leads to a pro-inflammatory status and hepatocellular death by apoptosis. Nevertheless, many pathophysiological factors still unknown. It is important to fully understand this mechanism to prevent the progression of liver fibrosis. Therapeutic targets targeted to interfere or treat lipotoxicity should be developed.

CONFLICT OF INTEREST STATEMENT

Authors disclose no conflict of interest.

AUTHORS' CONTRIBUTIONS

JCG, ME, NMS contributed to the conceptualization and the writing of the manuscript.

ABBREVIATIONS

NAFLD = Non Alcoholic Fatty liver disease

MAFLD = Metabolic Associated Fatty Liver Disease

T2DM = type 2 diabetes Mellitus

BA = Bile Acids

FFAs = Free Fatty Acids

TGs = Triglycerides

ER = Endoplasmic Reticulum

AT = Adipose Tissue

PPRA γ = peroxisome proliferator-activated receptor gamma

SREBP-1 = sterol-regulatory element binding protein

C/EBPs = CCAAT/enhancer-binding proteins

STATs = signal transducers and activators of transcription

KLF = Kruppel-like factor proteins

AP-1 = the activating protein 1

FABPpm = plasma membrane fatty acid binding protein

FATPs = Fatty acid Transport proteins

AT = adipose tissue

DGAT2 = enzyme diacylglycerol O-Acyltranferase 2

mTOR = mammalian target of rapamycin complex 1

mTORC1 = mammalian target of rapamycin complex 1

JNK = c-Jun-N-terminal kinase

DAMPs = damage-associated molecular patterns

TLR = toll liker receptors

NLRP3 = NOD like protein 3 inflammasone

LPCs = lysophospatidil cholines

LCAT = lecithin-cholesterol acyltransferase

SPT = serine palmitoyl-CoA transferase

FXR = farnesoid X receptor

CA = chicoric Acid

Insig-1 = insulin-induced gene 1

HMGR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase

CDKN1 = cyclin-dependent kinase inhibitor 1

CK6 = cyclin-dependent kinase 6

UDCA = Ursodesoxicolic Acid

OCA = Obeticholic Acid.

DPP4 = Dipeptidyl dipetidaase-4

SGLT-2 = Sodium-glucose cotransporter

EMPA = Empaglifozin

DAPA = dapaglifozin

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