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TOPIC HIGHLIGHT

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Pathogenesis and therapeutic approaches for non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease affects approximately one-third of the population worldwide, and its incidence continues to increase with the increasing prevalence of other metabolic disorders such as type 2 diabetes. As non-alcoholic fatty liver disease can progress to liver cirrhosis, its treatment is attracting greater attention. The pathogenesis of non-alcoholic fatty liver disease is closely associated with insulin resistance and dyslipidemia, especially hypertriglyceridemia. Increased serum levels of free fatty acid and glucose can cause oxidative stress in the liver and peripheral tissue, leading to ectopic fat accumulation, especially in the liver. In this review, we summarize the mechanism underlying the progression of hepatic steatosis to steatohepatitis and cirrhosis. We also discuss established drugs that are already being used to treat non-alcoholic fatty liver disease, in addition to newly discovered agents, with respect to their mechanisms of drug action, focusing mainly on hepatic insulin resistance. As well, we review clinical data that demonstrate the efficacy of these drugs, together with improvements in biochemical or histological parameters.

Key words: Non-alcoholic fatty liver disease; Insulin resistance; Drugs; Pathogenesis

Core tip: In this review, we summarize the pathogenesis underlying the progression of hepatic steatosis to steatohepatitis and cirrhosis. We also discuss established drugs that are already being used to treat non-alcoholic fatty liver disease, in addition to newly discovered agents, with respect to their mechanisms of drug action, focusing mainly on hepatic insulin resistance. As well, we review clinical data that demonstrate the efficacy of these drugs, together with improvements in biochemical or histological parameters. Furthermore, we introduced future treatment option for non-alcoholic fatty liver disease.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the accumulation of lipid within hepatocytes, is a common disease[1]. The worldwide prevalence of NAFLD is estimated to be 20%-30%[2], although increasing to 57%-74% among obese patients[3]. NAFLD refers to a wide spectrum of fatty degenerative disorders of the liver in the absence of alcohol intake, ranging from simple steatosis to steatohepatitis and cirrhosis[4]. Nonalcoholic steatohepatitis (NASH) is histologically characterized by inflammatory cell recruitment. NASH is a significant risk factor for hepatic cirrhosis, compared with simple steatosis[5], and 4%-27% of cases of NASH progress to hepatocellular carcinoma after the development of cirrhosis[6]. In one study, NAFLD was pres-

ent in 75% of obese [body mass index (BMI) ≥ 30 kg/m^2] patients, 16% of non-obese patients, and 34%-74% of patients with type 2 diabetes[7]. Another study reported diagnoses of fatty liver in 39% of obese (BMI ≥ 30 kg/m^2) patients, 41% of patients with known type 2 diabetes, and 32% of patients with dyslipidemia[8]. Patients with NAFLD are not only insulin resistant, but also tend to present with alterations in plasma triglyceride (TG) levels[9]. NAFLD is strongly associated with metabolic syndrome, especially insulin resistance, central obesity, and dyslipidemia. Therefore, NAFLD is regarded as a difficult to treat component of metabolic syndrome[10]. In this review, we investigate the mechanisms of hepatic fat accumulation, focusing on the role of insulin resistance therein, and review current therapeutic options and new candidate drugs for the treatment of NAFLD.

PATHOGENESIS

Insulin resistance - free fatty acid flux and hyperinsulinemia

Hepatic steatosis is caused by an imbalance in triglyceride movement through the liver cell. Triglyceride is composed of free fatty acid (FFA) and glycerol. Total FFA is derived from three sources, the diet (15%), *de novo* synthesis (26%), and circulating FFA (56%)[11]. A high-fat diet is known to lead to the development of hepatic steatosis. However, estimates suggest that approximately 60% of liver fat is derived from circulating nonesterified fatty acids (NEFAs) in individuals who eat a normal fat-containing diet[11]. Obesity is associated with insulin resistance and an elevated leptin level. In particular, increased visceral fat correlates with peripheral and hepatic insulin resistance[12,13]. Insulin resistance in skeletal muscle and adipose tissue results in increased levels of NEFAs through increased lipid oxidation in adipose tissue (Figure 1). Accordingly, NEFA flux plays an important role in hepatic fat accumulation[14]. An increase in hepatocellular diacylglycerol is associated with decreased tyrosine phosphorylation of insulin receptor substrate 2 (IRS-2)[15,16]. In turn, the decreased activity of IRS-2 and PI3K leads to increased hepatic glucose production[17]. Hyperinsulinemia also arises in response to insulin resistance in adipose tissue, leading not only to downregulation of IRS-2 in the liver, but also to a continued increase in the level of sterol regulatory element binding protein-1c (SREBP-1c) *via* the insulin signaling pathway involving AKT2, liver X receptor (LXR) and mammalian target of rapamycin[18,19]. Elevated levels of SREBP-1c up-regulate lipogenic gene expression, increase fatty acid synthesis, and accelerate hepatic fat accumulation[20]. Additionally, overexpression of SREBP-1c represses IRS-2 expression[21]. Glucose-stimulated lipogenesis is mediated by carbohydrate-responsive element-binding protein (ChREBP) in the liver. Like SREBP-1c, ChREBP increases lipogenesis by inducing lipogenic gene expression during consumption of a diet high in carbohydrates[22,23].

Endoplasmic reticulum stress

The endoplasmic reticulum (ER) is an intracellular organelle that plays an important role in the synthesis, folding, and trafficking of proteins. Cellular nutrient status and energy condition highly influence the function of the ER, and dysfunction in the ER causes accumulation of unfolded proteins therein, triggering an unfolded protein response (UPR)[24]. Under stress, such as hypoxia, inflammation and energy excess, UPR is characterized by adaptive cellular processes of increased degradation of proteins and translational arrest of protein synthesis to restore normal function of the ER. As well, UPR mediates metabolic and immune responses that aggravate insulin resistance[25-27]. Both PKR-like kinase and the α-subunit of translation initiation factor 2 (eIF2α), well-known ER stress markers, are increased in hepatocytes of ob/ob mice, compared with control mice[26]. Obesity causes ER stress that leads to suppression of insulin signaling through serine phosphorylation of insulin receptor substrate-1 (IRS-1) and activation of the c-Jun N-terminal kinase (JNK) pathway[26]. Among subjects with metabolic syndrome, those with NASH showed higher levels phosphorylated JNK protein, compared to subjects with simple hepatic steatosis. Furthermore, subjects with NASH did not generate spliced manipulation of X-box–binding protein-1 (sXBP-1), which is a key regulator in ER stress in relation to insulin action[24,26]. Additionally, weight reduction in obese subjects has been shown to induce improvement in ER stress *via* suppression of phosphorylated JNK and eIF2α in adipose tissue and the liver[28].

Role of oxidative stress - mitochondrial dysfunction

The two-hit hypothesis is a key concept of NAFLD pathogenesis. In fatty livers, simple hepatic steatosis (first hit) sensitizes the liver to inflammatory cytokines or oxidative stress (second hit), leading to development of steatohepatitis[29]. Oxidative stress is resulted from a serious imbalance between the limited antioxidant defenses and excessive formation of reactive species such as reactive oxygen species (ROS) or reactive nitrogen species (RNS)[30]. ROS is an integrated term that describes a variety of species of free radicals derived from molecular oxygen, such as superoxide, hydrogen peroxide, and hydroxyl[31]. In cells, mitochondria are a major source of ROS generation. The important factor modulating mitochondrial ROS generation is the redox state of the respiratory chain[32,33]. FFAs are metabolized *via* the mitochondrial β-oxidation pathway and the tricarboxylic acid (TCA) cycle, which generates citrate that in turn inhibits glycolysis. As a result, glucose oxidation and glucose uptake *via* glucose transporter type 4 (GLUT4) in skeletal muscle are reduced[34,35]. To compensate for the excessive fat storage in the liver, increased hepatic FFA uptake stimulates hepatic oxidation of fatty acids in obese individuals. Mitochondrial FFA oxidation is maintained until mitochondrial respiration becomes severely impaired[36,37]. However, accelerated β-oxidation not only causes excessive electron flux in the electron transport chain, but also leads to increased production of ROS, and can lead to mitochondrial dysfunction[38]. Excessive ROS production by mitochondria can lead to oxidative damage to

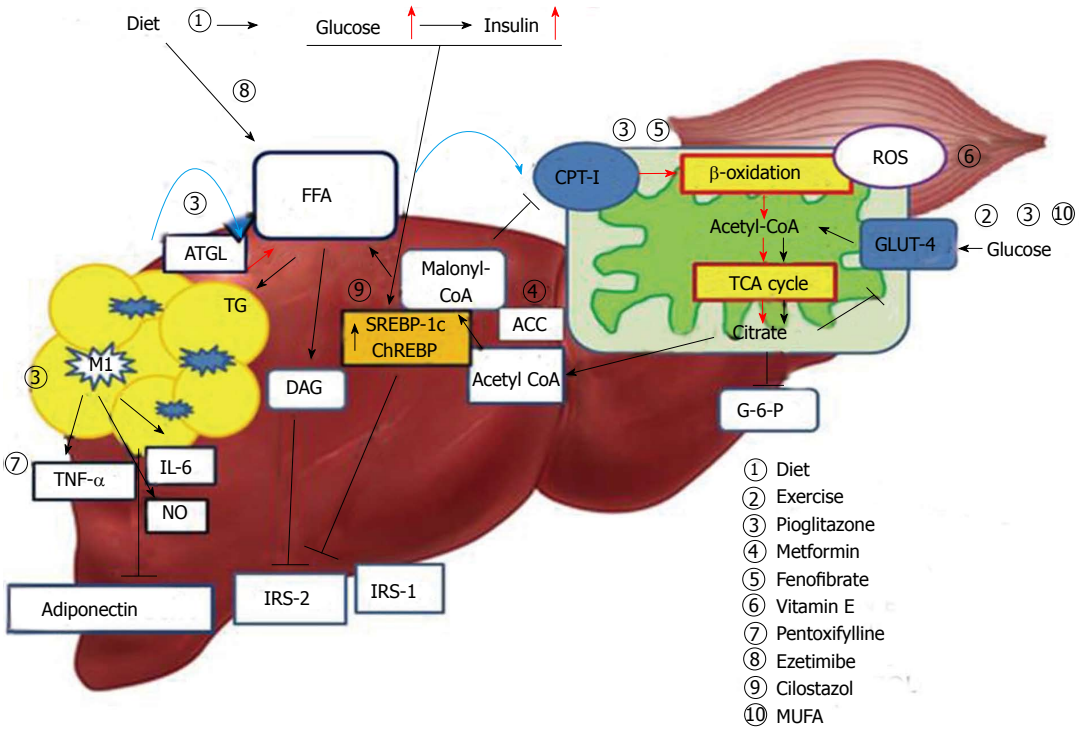

Figure 1 Mechanism of hepatic insulin resistance and the key pathway of drug action. Delivery of FFAs to the liver and skeletal muscle is increased in insulin resistance conditions, and these are metabolized *via* mitochondrial β-oxidation. Consequently, hyperglycemia and increased hepatic FFA uptake reduce glucose uptake and oxidation in skeletal muscle. Diet and exercise are the main treatment strategies for this pathogenesis; insulin sensitizers and MUFA may contribute to reducing peripheral insulin resistance. Pioglitazone and fenofibrate act on β-oxidation of mitochondria and reduce hepatic steatosis. Accelerated β-oxidation also causes increased production of ROS. Vitamin E can reduce oxidative stress. Adipose tissue inflammation of the liver leads to inflammatory activation of hepatic Kupffer cells via classic response (M1) and produce inflammatory cytokines. This is also associated with decreased adiponectin levels and promotes hepatic steatohepatitis. Pentoxifylline inhibits TNF-α and alleviates steatohepatitis. Hyperglycemia caused by insulin resistance up-regulates lipogenic gene expression, such as SREBP-1c and ChREBP, and induces lipogenesis in hepatocytes. Cilostasol may inhibit SREBP-1c. FFA: Free fatty acid; TG: Triglyceride; CPT- Ⅰ: Carnitine palmitoyltransferase-Ⅰ; ACC: Acetyl-CoA carboxylase; ATGL: Adipose triglyceride lipase; ChREBP: Carbohydrate responsive element binding protein; SREBP-1c: Sterol regulatory element binding protein-1c; TCA: Tricarboxylic acid; ROS: Reactive oxygen species; IRS: Insulin receptor substrate; DAG: Diacylglycerol; G-6-P: Glucose 6-phosphate; TNF-α: Tumor necrosis factor- α; MUFA: Monosaturated fatty acids; M1: Kupffer cells activated *via* classic pathway.

the mitochondrial membrane and DNA and can impair mitochondrial metabolic functions[33]. The increase in hepatic lipogenesis in NASH results in increased production of malonyl-CoA. Inhibition of carnitine palmitoyltransferase-I (CPT-1) by malonyl-CoA leads to decreased entry of long chain fatty acid into the mitochondria, and causes reduced β-oxidation and enhanced triglyceride accumulation in the liver[38-40]. The nuclear receptor peroxisome proliferator-activated receptor α (PPAR-α) plays an important role in the transcriptional control of many enzymes involved in mitochondrial fatty acid β-oxidation. Peroxisome proliferator-activated receptor-gamma coactivator (PGC) -1α cooperates with PPAR-α and regulates genes that encode mitochondrial fatty acid oxidation enzymes, such as CPT-1 and medium chain acyl-CoA dehydrogenase[40]. Previously, a PPAR-α-deficient mouse model showed a lack of hepatic peroxisome proliferation and dyslipidemia with obesity and hepatic steatosis[41].

Inflammation and adipokines

Overall obesity is correlated with NAFLD, and accumulation of intra-abdominal fat in particular is believed to play an important role in the development of insulin resistance[12,13]. Meanwhile, hepatic fat accumulation is associated with insulin resistance independent of intra-abdominal fat accumulation and overall obesity. Even in normal weight subjects, hepatic steatosis has been shown to be related to various parameters of insulin resistance, such as basal glucose level or serum FFA level[42]. In addition to being a major organ of triglyceride deposition, adipose tissue acts an endocrine organ that secretes several hormones[43]. Adipocytes secrete adiponectin and leptin, in addition to the other adipokines, such as retinol-binding protein, tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and plasminogen activator inhibitor-1[43]. Adiponectin stimulates phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) in the liver and muscles, thereby, increasing glucose utilization and fatty-acid oxidation[44]. In a previous study, serum adiponectin levels decreased with an increases in obesity, in particular increases in intra-abdominal fat mass[45,46]. In another study, adiponectin knockout mice fed a high-fat diet exhibited increased incidences of obesity, hyperinsulinemia, and steatohepatitis. These experimental data indicate that adiponectin may play a key protective role against the progression of NASH[47]. Reportedly, adipose tissue in obese individuals stimulates a shift in macrophage activation from the al-

Table 1 Treatment outcomes of variable regimens

Study	Treatment group	Control group	No.	Study design	Duration (mo)	Histology	Liver enzymes	US
Life style modification								
Huang *et al*[66]	Diet	-	12	Open label	12	Improved	-	-
Ueno *et al*[65]	Diet/Exercise	Control	15	Open label	3	Improved	Improved	-
Pioglitazone (insulin sensitizer)								
Promrat *et al*[71]	Pioglitazone	-	18	Open label	12	Improved	Improved	-
Belfort *et al*[72]	Pioglitazone and Diet	Placebo	55	RCT	6	Improved	Improved	-
Aithal *et al*[73]	Pioglitazone and diet/Exercise	Placebo	74	RCT	12	Improved	Improved	-
Sanyal *et al*[74]	Pioglitazone	Placebo	163	RCT	24	Improved	Improved	-
Metformin (insulin sensitizer)								
Garinis *et al*[100]	Metformin and Diet	Diet	50	RCT	6	-	-	Improved
Haukeland *et al*[103]	Metformin	Placebo	48	RCT	6	-	-	-
Uygun *et al*[101]	Metformin and Diet	Control	50	Open label	6	-	-	Improved
Bugianes *et al*[99]	Metformin	Diet	53	RCT	12	Improved	Improved	-
Bugianes *et al*[99]	Metformin	Vitamin E	57	RCT	12	-	Improved	-
Vitamin E (antioxidant)								
Bugianesi *et al*[99]	Vitemin E	Diet	55	RCT	12	-	-	-
Sanyal *et al*[74]	Vitamin E	Placebo	167	RCT	24	Improved	Improved	
Vajro *et al*[109]	Vitamin E	Diet	25	RCT	6	-	-	-
Other drugs								
Sanjay *et al*[112]	Pentoxifylline	-	18	Open label	6	-	Improved	-
Yoneda *et al*[127]	Ezetimibe	-	10	Open label	6	Improved	Improved	
Vasilios *et al*[118]	Statin	Control	437	Open label	36	-	Improved	-
Lindor *et al*[130]	UDCA	Placebo	166	RCT	48	-	-	-
Capani *et al*[138]	PUFA	Control	42	RCT	12	-	Improved	Improved

No.: Number; US: Ultrasonography; RCT: Randomized controlled trial.

ternative response (M2) to the classic response (M1), and these classically activated macrophages (CAMs) secrete a variety of inflammatory cytokines, such as TNF-α, IL-6, and NO[48]. Additionally, studies showed that inflammatory activation of hepatic Kupffer cells in ob/ob mice promotes hepatotoxicity, resulting in hepatic insulin resistance and steatohepatitis[49,50]. Thus, increases in TNF-α and IL-6 in obese subjects may play an important role in insulin resistance and hepatic steatosis[51,52].

Gut-microbial alternation and TLRs stimulation

As mentioned above, obesity is often associated with NASH and systemic inflammation characterized increases in inflammatory cytokine levels. Obesity also can cause increased intestinal mucosa permeability and endotoxin levels in portal circulation that can contribute to hepatocellular damage[53,54]. Kupffer cells in the liver play a key role in clearing endotoxin and are activated through Toll like receptor 2,3,4 and 9 signaling in the presence of endotoxin. In particular, activation of Toll like receptor4 (TLR4) is reportedly associated with stimulation of lipopolysaccharide (LPS)[55-57]. Previously, animal model studies showed that TLRs 2, 4 and 9 may contribute to the pathogenesis of NAFLD[55,58]. Activated Kupffer cells induce expression of pro-inflammatory cytokines, such TNF-α, IL-6, IL-18 and IL-12 as well as anti-inflammatory cytokines[59]. TLRs including TLRs 2,4 and 9 are activated *via* a MyD88 dependent pathway. This pathway consists of the activation of serine kinase IL-1R-associated kinase and TBF-receptor-associated factor 6 and is involved in the activation of the transcription factor NF-κB, which is related to inflammatory cytokine production[60].

TREATMENT

Life style modification - diet and exercise

Weight loss due to diet and exercise has been demonstrated to alleviate hepatic steatosis[61]. Body weight reduction and exercise are important independent factors for improvement of hepatic steatosis[62]. In obese women, hepatic fat content measured by magnetic resonance imaging was shown to decrease in response to weight loss interventions[63]. Several studies have shown a significant reduction in alanine transaminase (ALT) levels and improvement in biochemical markers following intervention with a calorie-restricted diet combined with exercise[63,64]. A few studies have also shown histologic improvement with increased exercise and weight reduction[65,66] (Table 1). Exercise improves insulin sensitivity in skeletal muscle *via* GLUT4 expression and increases glucose utilization. Thus, exercise decreases levels of serum glucose and insulin[67]. An improvement in hyperinsulinemia can result in decreased liver fat mass, because hyperinsulinemia stimulates hepatic steatosis *via* the SREBP-1c pathway[19]. In particular, NAFLD patients with metabolic syndrome show a great improvement in hepatic steatosis after weight loss[68].

Insulin sensitizer-thiazolidinedione, metformin

Thiazolidinedione: Thiazolidinediones (TZDs) are insulin-sensitizing agents that have been shown to improve not only hepatic steatosis, but also whole body insulin resistance[69]. Improvements in insulin resistance and histologic and biochemical parameters were reported with TZD treatment[70-74]. Rosiglitazone is one TZD and is as-

sociated with an increased risk of myocardial infarction and cardiovascular death[75]. Meanwhile, pioglitazone is regarded as safe in regards to cardiovascular outcomes and is not associated with increased cardiovascular risk[76,77]. In patients with type 2 diabetes, pioglitazone has been recommended for the treatment of steatohepatitis proven by liver biopsy; however, its role in non-diabetic patients has not been established. The American Association for the Study of Liver Disease (AASLD) introduced pioglitazone as a first-line treatment of NAFLD in patients with type 2 diabetes[78]. TZDs increase glucose utilization of peripheral tissue and improve whole body insulin sensitivity as measured by the hyperinsulinemic euglycemic clamp technique, in patients with type 2 diabetes. Moreover, serum adiponectin levels increase and serum insulin levels decreases after treatment with pioglitazone[79,80]. An increase in serum adiponectin contributes to alleviation of hepatic steatosis and improves hepatic and peripheral insulin resistance[79]. As mentioned above, adiponectin increases lipid oxidation of FFA by ACC phosphorylation in the liver[44], and promotes the activation of anti-inflammatory M2 macrophages rather than M1 macrophages[81]. Obesity is closely related to an increase in NAFLD risk[82]. Increased levels of inflammatory adipose tissue macrophages (ATMs) and their secreted cytokines in a mouse model were shown to be related to systemic insulin resistance, which is associated with NAFLD development[15,83]. According to previous studies, ATMs are increased in obese subjects[84], and pioglitazone treatment results in not only a decrease in ATM content, but also in the inflammatory markers, TNF-α, IL-6, and inducible nitric oxide synthase (iNOS)[85,86]. TZDs also promote the alternative activation of monocytes into macrophages with anti-inflammatory properties, as opposed to the pro-inflammatory phenotype[87]. Although the pathogenesis of NAFLD development is closely related to obesity, the distribution of fat is more important than overall obesity. Excessive visceral fat accumulation plays an important role in the development of insulin resistance and NAFLD by acting as a source of FFA[12]. Pioglitazone is strongly associated with fat redistribution, increases in subcutaneous fat area decreases in visceral fat area (visceral to subcutaneous fat ratio)[88]. Another study showed that the ratio of visceral fat thickness to subcutaneous fat thickness decreases after pioglitazone treatment and is correlated with a change in high sensitivity C-reactive protein levels[89]. TZD treatment results revealed a decrease in serum FFA levels, which in turn reduced FFA supply to the liver and led to a decrease in hepatic triglyceride content[90]. Recent studies have focused on the role of sirtuin-6 (SIRT-6) in the glucose and lipid metabolism associated with TZDs. TZD treatment reduced hepatic fat accumulation and increased expression of SIRT-6 and PGC1-α in rat livers[91]. Also, liver-specific SIRT-6 knockout mice exhibited fatty liver formation[92], leading to NASH[93].

Metformin: Metformin improves insulin resistance and hyperinsulinemia by increasing peripheral glucose uptake and decreasing hepatic gluconeogenesis[94]. Metformin activates AMP kinase *via* a LKB-1 dependent mechanism in skeletal muscle. Also it can activate AMPK by stimulating AMP accumulation in hepatocytes. The increase in AMP interferes with glucagon action and decreases cAMP levels, leading to decreased production of hepatic glucose[95,96]. Activation of AMPK results in decreased hepatic triglyceride synthesis and increased fatty acid oxidation[97], as well as attenuated hepatic steatosis due to decreased SREBP-1c activity[98]. A randomized controlled trial showed that subjects treated with metformin exhibit significant improvement in ALT levels, compared with those who were on a restricted diet or were treated with vitamin E, as well as improvements in histology after a 12 mo of treatment[99,100]. Many studies have shown that metformin treatment normalizes transaminase levels and decreases hepatic steatosis as determined by follow-up ultrasound; nevertheless, histologic data remain limited[100-103]. As NASH is closely associated with development of HCC and liver fibrosis, metformin may be limited in the reduction of these severe outcomes, including mortality[104].

Antioxidant - vitamin E (α-tocopherol), pentoxifylline

As mentioned above, oxidative stress contributes to the progression of NASH from simple hepatic steatosis. A recent study reported that subjects who were treated with vitamin E (α-tocopherol) showed improvement in hepatic steatosis and serum aminotransferase levels compared to a placebo group[74]. Vitamin E (α-tocopherol) has been used to treat non-diabetic NASH patients diagnosed by liver biopsy[78]. Meta-analyses of vitamin E have revealed an increase in all-cause mortality with high dose (≥ 400 IU/d) vitamin E supplement use, especially in subjects with chronic disease or at high risk for cardiovascular disease events, such as type 2 diabetes. However, these results are uncertain in healthy subjects[105,106]. Two pilot studies reported improved ALT levels with vitamin E treatment[107,108]. However, two randomized controlled trials failed to show the efficacy of vitamin E treatment in NAFLD[109,110]. Pentoxifylline, a TNF-α inhibitor, has also been considered for the treatment of hepatic steatosis, since it plays an important role in the progression of simple hepatic steatosis to steatohepatitis. In previous studies, administration of pentoxifylline generated improvements in biochemical markers, such as aminotransferase and Homa-IR, in patients with NASH[111,112]. Nevertheless, further study is needed to prove the efficacy of pentoxifylline with respect to histologic improvement of NAFLD.

Lipid-lowering agents - fibrates, ezetimibe and statins

Hypertriglyceridemia is a major component of metabolic syndrome and is strongly associated with NAFLD. Increased FFA delivery to the liver causes accumulation of hepatic fat[9]. Many different lipid-lowering agents have been investigated for the treatment of NAFLD. Patients treated with gemfibrozil, one type of fibrate, showed decreased ALT levels, compared to the control group[113]. However, clofibrate did not show a beneficial effect on

NAFLD[114]. PPAR-α modulates not only FFA transport and β-oxidation to decrease triglyceride in hepatocytes, but also glucose and amino acid metabolism in liver and skeletal muscle. PPAR-α activation is involved in lipoprotein metabolism by increasing lipolysis, thus reducing the production of triglyceride-rich particles[115]. Fenofibrate increased levels of PPAR-α and decreased hepatic steatosis in an APOE2KI mouse model that represented diet-induced NASH[116]. A prospective study using atorvastatin reported significant reductions in serum transaminase level[117,118]. Atorvastatin induces hepatic low-density lipoprotein receptor-related protein 1 (LRP-1) that plays an important role in clearance of circulating triglyceride in the liver[119]. In disposal of chylomicron in hepatocytes, interaction of LRP-1 receptors and ApoE play important roles[120]. Thus, ApoE-deficient mice showed development of hepatic steatosis even when they were fed a normal chow-diet. Accordingly, ApoE may play a key role in intracellular metabolism and control of VLDL production by hepatocytes[121]. Statins are very important drugs to treat dyslipidemia in subjects with both insulin resistance and NAFLD. However, there is continued concern about the use of statins in subjects with established liver disease. According to several randomized controlled studies and retrospective studies, statin rarely induces serious liver injury[122-125]. Ezetimibe, a potent inhibitor of cholesterol absorption, has been reported to improve hepatic steatosis in obese Zucker fatty rats[126]. In a randomized controlled study, six months of treatment with ezetimibe led to improvements in serum ALT levels and histologic observations[127,128].

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is widely used in subjects with abnormal liver function. Several studies have investigated the efficacy of UDCA as a treatment drug of NAFLD, reporting that UDCA treatment attenuated hepatic steatosis, including histologic improvement[114,129,130]. However, in a placebo controlled, randomized control trial, UDCA exhibited limited efficacy in histologic improvement in subjects with NASH and improvements in liver enzyme did not differ in the UDCA group, compared to the placebo group[130]. Accordingly, AASLD does not recommend UDCA for the treatment of NAFLD[78].

Other treatment options - future candidates

Cilostazol: SREBP-1c is a key regulator of lipogenic gene expression in hepatocytes. Recent data have shown that cilostazol, a selective type Ⅲ phosphodiesterase inhibitor, inhibits SREBP-1c expression *via* the suppression of LXR and Sp1 activity[131]. Cilostazol also decreases serum triglyceride levels by increasing lipoprotein lipase (LPL) activity in STZ-induced diabetic rats[132]. Also, experimental data show that cilostazol stimulates LRP1 promoter activity in hepatocytes, leading to increased hepatic LRP1 expression[133]. In a study that used two experimental NAFLD models, both high-fat/high-calorie (HF/HC) diet mice and the choline-deficient/L-amino acid-defined (CDAA) diet mice, cilostazol generated improvement in hepatic steatosis in both mice models[134]. Cilostazol exhibits the potential for improvement of hepatic steatosis, and further data on its role in NAFLD are needed.

Polyunsaturated fatty acids and monounsaturated fatty acids: Polyunsaturated fatty acids (PUFAs) are found primarily in safflower, corn, soybean, cottonseed, sesame, and sunflower oils. Omega-3 fatty acids are representative of PUFA. A marked increase in long-chain PUFA n-6/n-3 ratio is observed in NAFLD patients and is associated with increased production of pro-inflammatory eicosanoids and dysregulation of liver and adipose tissue function[135]. PPAR-α activity is impaired in conditions in which levels of circulating n-3 PUFA are decreased and the n-6/n-3 fatty acid ratio is increased[136,137]. Treatment with n-3 PUFA was shown to improve biochemical parameters and alleviated hepatic steatosis by ultrasound follow-up[138,139]. Monounsaturated fatty acids (MUFAs) are comprised in olive oil. In a rat model, supplementation with MUFA resulted in improved insulin sensitivity, compared to rats fed a saturated fatty acid (SFA) diet. Additionally, GLUT4 translocation in skeletal muscle was decreased in rats fed a SFA diet, but not in those fed a MUFA diet. Increased GLUT4 translocation is related to an improvement in insulin sensitivity[140]. In obese rats, MUFA diet attenuated hepatic steatosis and altered hepatic fatty acid levels[141]. The beneficial effects of dietary MUFA in NAFLD patients should be investigated.

GLP-1 analogue: Exenatide is the synthetic form of exendin4 and it stimulates endogenous insulin secretion, leading to decreases in blood glucose. In one animal study, treatment of exendin4 resulted in a decrease of hepatic fat content, as well as reduction of fatty acid synthesis, in the liver of ob/ob mice[142]. In patients with type 2 diabetes, an exenatide treatment group showed greater improvements in liver enzymes, attenuating hepatic steatosis, than the metformin treatment group. However, this study had limitations of a lack of histologic confirmation of the liver[143]. To prove the efficacy of glucagon like peptide-1 (GLP-1) analogue in treatment of NAFLD, randomized controlled trials over a longer period are required.

MK615: MK615 is extracted from Japanese apricots, and can suppress the production of inflammatory cytokines such as TNF-α and IL-6 by inactivating NF-κB[144,145]. MK615 is regarded as a hepatoprotective agent, as it has been shown that a MK615 treatment group exhibited greater decreases in liver enzyme levels, compared with control groups. In rat models, MK615 treatment mice showed more improved liver histology than control mice[146]. Thus, further studies are required to clarify the effects of MK615 in subjects with NAFLD.

CONCLUSION

NAFLD is a common disease that can progress to liver cirrhosis. Moreover, NAFLD is strongly associated with type 2 diabetes and insulin resistance. NAFLD is the

result of complex interactions among diet, metabolic components, adipose tissue inflammation, and mitochondrial dysfunction. The pathogenesis of hepatic steatosis has not yet been fully determined. In this review, we outlined previously known mechanisms of NAFLD, as well as introduced new mechanisms that have been recently discovered. Above all, we reviewed the mechanisms of drugs matched to the pathogenesis of NAFLD. Furthermore, we introduced future treatment option for NAFLD. TZDs play a key role in restoring insulin sensitivity and decreasing adipose tissue inflammation, generating histologic improvements in hepatic steatohepatitis. Pioglitazone can be used to treat NASH in patients with type 2 diabetes with biopsy-proven NAFLD; meanwhile, non-diabetic patients can be treated with vitamin E. Metformin is a well-known insulin sensitizer; however, further study is needed to prove histologic improvements in patients with NAFLD. Additionally, the cholesterol-lowering agent ezetimibe has also shown histologic improvements. Cilostazol acts on SREBP-1c and can improve dyslipidemia; however, further research is needed to clarify the relationship between NAFLD and cilostazol. Finally, there is an outstanding need for effective preventive and therapeutic regimens to overcome NAFLD.

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