BMB
Reports

BMB Rep. 2016; 49(3): 139-148
www.bmbreports.org

Invited Mini Review

The role of lipids in the pathogenesis and treatment of type 2 diabetes and associated co-morbidities

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In the past decade, the incidence of type 2 diabetes (T2D) has rapidly increased, along with the associated cardiovascular complications. Therefore, understanding the pathophysiology underlying T2D, the associated complications and the impact of therapeutics on the T2D development has critical importance for current and future therapeutics. The prevailing feature of T2D is hyperglycemia due to excessive hepatic glucose production, insulin resistance, and insufficient secretion of insulin by the pancreas. These contribute to increased fatty acid influx into the liver and muscle causing accumulation of lipid metabolites. These lipid metabolites cause dyslipidemia and non-alcoholic fatty liver disease, which ultimately contributes to the increased cardiovascular risk in T2D. Therefore, understanding the mechanisms of hepatic insulin resistance and the specific role of liver lipids is critical in selecting and designing the most effective therapeutics for T2D and the associated co-morbidities, including dyslipidemia and cardiovascular disease. Herein, we review the effects and molecular mechanisms of conventional anti-hyperglycemic and lipid-lowering drugs on glucose and lipid metabolism. [BMB Reports 2016; 49(3): 139-148]

INTRODUCTION

Intake of high-calorie food and sedentary lifestyle are factors contributing to the worldwide outbreak of metabolic diseases including obesity and type 2 diabetes (T2D) (1). An epidemic increase in metabolic diseases is forecasted to occur within the next decade (2). T2D and obesity are closely associated with one another. Both increase the risk of cardiovascular diseases (CVD), the leading cause of death in diabetic subjects (3). Since T2D is defined as hyperglycemia, the aim of diabetes management has been focused to reduce fasting blood glucose concentrations to normoglycemic range (~4 to 6 mmol/L). However, while the glucose-centric view of anti-diabetic treatments benefit microvascular complications associated with T2D, this view has limitations in fixing the underlying pathophysiology of the disease: insulin resistance (4).

Although, glucose is the key aspect of T2D, one often overlooked feature is the relationship between glucose control and its impact on lipids (5). Furthermore, lipids and glucose fluxes are closely interlinked through the intersection of metabolic pathways at acetyl-CoA formation. The perturbation of one pathway can indirectly affect another pathway. Given the association among lipids, insulin resistance, T2D and CVD, understanding the pathophysiology of T2D development from both glucose and lipid-view is critical to allow the discovery of the best targets for future therapeutics for T2D and its comorbidities.

In this review, we summarize the molecular mechanisms and the relationship between lipids and the pathogenesis of T2D and CVD. We also address the impact of T2D therapies on hepatic and circulating lipids. Last, we assess the impact of lipid therapies on glucose homeostasis.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES AND ASSOCIATED CVD

Insulin resistance in the pathogenesis of T2D

Although the lack of insulin production and secretion by pancreatic β-cells are contributing factors to fasting hyperglycemia at later stages of T2D, insulin resistance is a factor that significantly contributes to the early development and progression into T2D (6). Insulin resistance is defined as diminished insulin signaling in normally insulin-responsive tissues such as liver, muscle, and adipose. The main traits of insulin resistance are decreased glycogen synthesis and glucose uptake in skeletal muscle (7, 8), defects in glycogen synthesis, and increased rates of gluconeogenesis in liver (9, 10). Skeletal muscle has been implicated as the predominant site of insulin-mediated glucose uptake during the postprandial stage in non-diabetic tissue (11). In contrast, during the fasting state, hepatic gluconeogenesis has been considered a main determinant for fasting plasma glucose concentrations and is de-

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http://dx.doi.org/10.5483/BMBRep.2016.49.3.268

Received 25 December 2015

Keywords: Cardiovascular disease, Diabetic dyslipidemia, Lipid metabolites, Insulin resistance, Type 2 diabetes

ISSN: 1976-670X (electronic edition)
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termined, in part by plasma insulin concentrations (12). Insulin resistance in adipose tissue also has a significant contribution to hyperglycemia since adipose tissue is the major storage site of gluconeogenic substrates and energy, like fatty acids and glycerol. Thus, elevated lipolysis can increase hepatic gluconeogenesis (13). In addition, pathologically increased fatty acid influx into the liver induces aberrant increases in intracellular lipids. Accumulation of specific lipid metabolites contributes to lipid-induced hepatic insulin resistance. Increased intracellular lipids also leads to hyperglycemia, as well as diabetic dyslipidemia associated with increased CVD risk (14).

Molecular mechanisms of lipid-induced insulin resistance

Mounting evidence has indicated that elevated intracellular lipid metabolite concentrations are associated with diminished insulin sensitivity in both liver and skeletal muscle. The specific molecular mechanism of lipid-induced insulin resistance has been thoroughly reviewed in previous papers (15-17). Excessive accumulation of toxic lipid metabolites, such as diacylglycerol (DAG) and ceramide species, provide a putative causal link between increased tissue lipids and hepatic insulin resistance via modulating insulin signaling (16, 17). DAG reduces insulin-stimulated phosphorylation of IRS2 and IRS2-associated PI(3)K activity through protein kinase-C epsilon (PKCε) activation. Additional data demonstrates ceramide inhibits phosphorylation of Akt2 (17). Both DAG and ceramide result in the impaired action of insulin to activate glycogen synthesis and suppress gluconeogenesis. The crucial role of PKCε in mediating lipid-induced hepatic insulin resistance has been demonstrated by knocking down expression of PKCε in the liver using an antisense oligonucleotide in rodents (18). In human subjects, intrahepatic DAG content had the best correlation with hepatic insulin resistance compared to other lipid intermediates such as hepatic ceramide, acylcarnitines or inflammatory markers. However, these data do not necessarily show causation (19).

Alternatively, ceramide or other sphingolipids metabolites are also hypothesized to contribute to the pathogenesis of T2D and CVD, because they disrupt insulin sensitivity, pancreatic β cell function and vascular reactivity (17). In a rodent model, hepatic ceramide content increased in rodents fed a high-fat diet (20). Reducing tissue ceramide content can, in certain cases, ameliorate insulin resistance and steatohepatitis (17, 21). Although, the causal role of ceramide remains to be tested using transgenic model, human studies demonstrate ceramide content is positively associated with metabolic diseases in various tissues such as muscle, plasma, and adipose tissue (22, 23). Elevated intracellular lipid metabolite concentrations have crucial roles in the pathogenesis of metabolic diseases including T2D, Non-alcoholic fatty liver disease (NAFLD), and CVD.

Type 2 diabetes and its co-morbidities including dyslipidemia, CVD and Nonalcoholic Steatohepatitis (NASH)

T2D and its associated vascular complications are not independent diseases and are linked in part by dyslipidemia. Diabetic dyslipidemia resulting from lipotoxicity is a state characterized by changes in the lipid profile, including increases in triglycerides and in lipid metabolites such as DAG, ceramides, free fatty acids, low density lipoprotein (LDL) cholesterol, and low level of high density lipoprotein (HDL) cholesterol (24). Although the precise mechanisms for dyslipidemia in diabetes are not known, insulin resistance contributes to the underlying pathophysiological causes in addition to over-nutrition and obesity (14). In the liver, concomitant with impaired insulin action on glucose metabolism, lipogenesis remains unaffected (25). Therefore, unsuppressed hepatic glucose production along with increased lipogenesis likely worsens the development of hepatic steatosis and dyslipidemia (16). In other words, insulin resistance can cause both tissue and circulating lipid abnormalities, thereby partially linking diabetic dyslipidemia to increased CVD risk.

Dyslipidemia is a contributing mechanism by which insulin resistance increases CVD risk in T2D individuals (26). Excessive production of very low density lipoproteins (VLDLs) in the liver and increased adipocyte free fatty acid flux from lipolysis under insulin resistant conditions also result in tissue and circulating lipid abnormalities. Since insulin is critical in the inhibition of hepatic VLDL formation in the liver and lipolysis in adipose tissue (14, 27), recovery of insulin action in these tissues is one of the key strategies to deal with abnormal lipid profiles found in T2D patients.

Hepatic steatosis, defined as excessive hepatic fat deposition, is a common co-morbidity of T2D and obesity (28). Although often considered a benign condition that can be stable over decades, the accumulation of hepatic fat is thought to be a pre-requisite for the development of NASH and the development of hepatic fibrosis (29). Additionally, studies suggest NAFLD is an independent risk factor for CVD (30). NASH was reported in ~12% of the United States population, while ~46% of the Unites States population was found to have NAFLD (31). T2D is thought to accelerate the progression of NASH and fibrosis through the effects of hyperglycemia, inflammation, and lipid overload. Therefore, targeting tissue lipid has the potential to treat T2D and its co-morbidities.

THE EFFECT OF CURRENT TYPE 2 DIABETES THERAPIES ON LIPIDS

Metformin

Metformin is currently the standard of care for glycemic control in diabetic patients (32). Metformin alleviates hyperglycemia via suppression of hepatic gluconeogenesis and enhancement of tissue glucose uptake (33, 34). In terms of glucose and lipid homeostasis, pre-clinical studies show that metformin increases AMP-activated kinase (AMPK) phosphorylation and downstream responses of glucose and hepatic lipid regulation, including cholesterol and triglycerides (35, 36). However, clinical studies investigating the use of metformin have shown

minimal benefits on LDL cholesterol and triglycerides, when correcting for glucose control in diabetic patients (37). Furthermore, in patients with defined NASH, no histological changes were observed following a 52-week NASH trial in non-diabetics with insulin resistance (38).

The extent of AMPK activation and reduction of lipids by metformin in pre-clinical trials may be due to the use of supra-pharmacological doses resulting in metformin circulating concentrations greater than 1 mM (39). Although, many studies have demonstrated some clinical benefits on NAFLD and reductions in circulating liver enzymes, metformin mechanistically and clinically appears to have limited benefits in reversing the pathophysiology of NASH patients. The lack of robust translatability of the impact of metformin on lipids from the pre-clinical mechanistic work to the clinical setting may be due to the supra-pharmacological doses used in the pre-clinical trials. Multiple studies have shown the glycemic effect of metformin occurs independently of AMPK activation. Recently, the specific molecular mechanism of metformin inhibition of hepatic gluconeogenesis has been proposed to occur by non-competitive inhibition of mitochondrial glycerophosphate dehydrogenase 2 through effects on the redox state (39). The impact of this redox cycle inhibition on lipids is still under analysis.

Thiazolidinediones (TZDs)

TZDs were initially discovered at Takeda as molecules to improve metabolism and have been subsequently described in publications since 1983 (40). TZDs exert their metabolic benefits as agonists of the nuclear hormone receptor, peroxisome proliferator-activated receptor gamma (PPAR-gamma), which controls a variety of key metabolic processes such as insulin sensitivity, adipogenesis, and lipid metabolism (41). TZDs induce sustained and well controlled glycemic balance through insulin sensitization. PPAR-gamma is primarily expressed in white adipose tissue. Activation of PPAR-gamma causes adipogenesis, increases in mitochondrial respiration, and browning of adipose tissue (42, 43). These molecular mechanisms resulted in controlling effects on plasma glycemia and a more durable glycemic control when compared to metformin and sulfonylureas (44).

Regarding the lipid control, TZDs have substantial benefits on hepatic lipids as demonstrated in numerous clinical studies. In a trial in subjects with T2D and defined NASH, pioglitazone treatment was found to normalize circulating plasma ALT and AST concentrations, as well as, reduce hepatic fat concentrations by 54% (45). Subsequently, the PIVENS trial investigated the use of Vitamin E or pioglitazone for the treatment of NASH in non-diabetics. Although the primary endpoint, after 52 weeks in subjects treated with pioglitazone, did not reach statistical significance for histological improvements in NASH (46), secondary endpoint scores were met, as in reduction in steatosis, lobular inflammation, and reduction in the non-alcoholic fatty liver disease. Furthermore, in the FLIRT trial, which evaluated rosiglitazone for the treatment of NASH, found an improvement in steatosis. However, there were no additional benefits on other histological endpoints (47).

The molecular mechanisms behind the reduction of hepatic triglycerides and improvements in NASH observed with subjects treated with TZDs are evolving. One hypothesis is the "lipid steal" model in which TZDs cause adipose tissue expansion through the formation of mature adipocytes from adipose tissue progenitor cells and the browning of mature adipocytes through the stabilization of PRDM16. In another study, TZDs are shown to function by sequestering lipids in adipose tissue rather than in the liver (48).

According to results from Reitman and colleagues, white adipose tissue is the most important site for lipid sequestration under TZD treatment (42). A-ZIP/F-1 mice, which do not have adipose tissue, exhibit lipid accumulation in the liver similar to lipodystrophic diabetes, while implantation of adipose tissue to A-ZIP/F-1 mice improve hepatic steatosis (42). Consequently, TZD treatment induces hepatic lipid reduction related to the possibility of improvements in insulin resistance. A second hypothesis for reduction of hepatic steatosis by TZD is through the activation of PPAR-gamma in white adipocytes, which allows the dysfunctional adipose tissue found in diabetes and the metabolic syndrome, to be returned to functional adipose tissue for the storage of lipids. This in turn reduces the circulating free fatty acids and the fat content in muscle and liver tissue.

An alternative hypothesis is through the off target inhibition of MCP1 and MCP2, the mitochondrial pyruvate carrier transporter, by TZDs. Specific deletion of MPC in the liver has led to pyruvate-alanine cycling and reductions in hepatic gluconeogenesis (49). Development of specific MCP inhibitors is currently in clinical trials for T2D and NASH (50). Signs of PPAR-gamma activation, water retention, and increases in circulating adiponectin were also observed in some of these clinical studies (50). MCP inhibitors devoid of PPAR-gamma activity will be needed to determine the specific impact of MCP inhibition on lipids and glucose.

Although, a potent insulin sensitizer, prescriptions of TZDs have decreased due to safety concerns, such as bone fractures and potential cancers, in addition to the less desirable effects on edema and weight gain (41).

Sulfonylurea (SU)/Insulin

Sulfonylurea (SU) is an insulin secretagogue, which binds to the ATP-sensitive K^+ channel and facilitates insulin secretion. The use of SU is associated with robust reductions in HbA1c; however, the durability of therapeutic effect by SU treatment has been questioned (51). By stimulating insulin secretion, SU treatment exhibits improvement in glycemic control, including suppression of hepatic gluconeogenesis, which results in reduced fasting blood glucose concentrations. However the use of SU agents is associated with increased hypoglycemia risk (52).

In terms of effects on lipids, it was reported that SU agents have the ability to reverse the abnormal lipid composition of

diabetics including the high triglyceride:ApoB ratio (53). During SU therapy, triglyceride production and the triglyceride:ApoB ratio were reduced and VLDL clearance rate improved (53). In an additional study, total cholesterol and LDL cholesterol were markedly reduced with an increase in the HDL:LDL cholesterol ratio (54). However, larger studies failed to show significant effects on triglycerides in patients treated with SU (55).

Basal insulin, such as glargine, has been a mainstay in type 1 and 2 diabetes since the early 2000s. In meta-analyses, basal insulin exhibited modest reductions in LDL cholesterol and triglycerides. However, there was no cardiovascular benefit in subjects treated with basal insulin in the Outcome Reduction With Initial Glargine Intervention (ORGIN) trial (56).

Glargine was shown to reduce the total liver fat index in a 12-week study in patients with poorly controlled T2D. The mechanism behind the effects of SUs and insulin on lipids is presumably through the inhibitory effect of insulin on adipose tissue lipolysis and increased clearance of TG-rich chylomicrons through the activation of lipoprotein lipase (LPL).

Glucagon-like peptide-1 (GLP-1) and Dipeptidyl peptidase-IV (DPP-IV) inhibitors

Gut derived glucagon-like peptide-1 (GLP-1) is an insulin secretion stimulator that promotes insulin action. Although the direct effect of GLP-1 on human hepatocytes is controversial, GLP-1 treatment improves hepatic steatosis in diet-induced obesity (DIO) and in genetically obese models. In human, GLP-1 treatment caused significant reductions in hepatic triglycerides in longer clinical studies (57-59). The key mode of action of GLP-1 is an increase of cyclic AMP (cAMP) levels in hepatocytes, which leads to downstream activation of AMPK in the liver. Activation of AMPK directly regulates transcription of SREBP-1c and in turn, lipogenic downstream genes, such as acetyl-CoA carboxylase, fatty acid synthase, and stearoyl-CoA desaturase-1 are down-regulated; although the detection of the GLP-1 receptor on human hepatocytes has been controversial.

Therefore, in pre-clinical studies, steatosis is resolved with direct activation of GLP-1 receptor. Additionally to NAFLD, liraglutaide, a long acting peptide GLP-1 agonist, was shown to be safe and efficacious in patients with non-alcoholic steatohepatitis in the LEAN trial. In this trial, 39% of overweight patients with clinical signs of NASH treated with 1.8 mg of liraglutade resolved their NASH compared to only 9% in the placebo group (60). Liraglutide has also been shown to positively influence circulating triglycerides (61).

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are oral hypoglycemic, which inhibit a deactivation of glucagon-like peptide-1 (GLP-1). Due to its close relationship with GLP-1, the DPP-IV inhibitor mechanism of action was proposed to be by increasing insulin secretion. However, precise mode of action of DPP-IV inhibitors remains unclear. Recently, it has been demonstrated that GLP-1 or DPP-IV treatment causes AMPK activation through an increase in cAMP (57). Since AMPK phosphorylation directly prevents hepatic lipogenesis, this provides a clear explanation of the results from pre-clinical and clinical studies.

Aroor *et al*. showed that DPP-IV inhibitor treatment in the DIO model rescued insulin resistance and significantly reduced triglycerides, DAG, and certain fatty acid species content (62). Furthermore, hepatic triglyceride secretion was reversed by a DPP-IV inhibitor (62). Pre-clinical data is also consistent with results from human clinical studies, concerning hepatic lipid content (63, 64). DPP-IV agents have not shown any cardiovascular benefit and some DPP-IV inhibitors are associated with increased hospitalization due to heart failure (65). Although GLP-1 and DPP-IV both show substantial positive effects on hepatic lipids, its cardiovascular benefit has yet to be demonstrated.

Sodium/Glucose co-transporter 2 (SGLT2) inhibitors

SGLT2 inhibitors are a new class of anti-diabetic drugs which lower blood glucose by inhibition of glucose reabsorption in the renal proximal tubule through SGLT2 (66). Although SGLT2 inhibitor treatment brings about reduction of insulin secretion and increased endogenous glucose production as a counter-regulatory response to therapeutic glycosuria, this therapy improves pancreatic β-cell function, insulin action (66), and shifts the substrate utilization to lipids in the case of chronic treatment (67, 68).

Yokono *et al*. investigated the effects of ipragliflozin, a SGLT2 inhibitor, on lipid metabolism in rats fed high fat diets (68). Under treatment, visceral and subcutaneous fat masses decreased and lipid utilization concomitant with effects on lipolysis and fatty acid oxidation improved (68). In the clinical setting, SGLT2 inhibition was shown to cause a modest reduction in body weight and blood pressure, although there were increases in circulating LDL concentrations (69, 70). Recently, patients administered empagliflozin at either 10 mg or 25 mg showed improvement in cardiovascular outcomes and death from any cause (71). The molecular mechanisms behind the improvement in cardiovascular outcomes are still being elucidated.

Glucokinase activators and glucagon antagonists

Both hepato-selective and systemic glucokinase activators have been developed for T2D along with glucagon antagonists in an attempt to rebalance the insulin:glucagon ratio/signaling and to reduce hepatic glucose output (72, 73). Glucokinase activation in the β-cell increases insulin secretion, however, is associated with lack of durable efficacy and inappropriate insulin secretion resulting in hypoglycemia. To circumvent these issues, hepato-selective glucokinase activators were developed to have glycemic control. Unfortunately, they were associated with increased circulating plasma triglycerides (74).

Studies from pre-clinical models showed that increased plasma triglycerides were likely due to increased secretion due to activation of the lipogenic transcription factor, carbohydrate-responsive element-binding protein (74). Pre-clinical studies

using this compound made by Pfizer, predicted minimal changes in hepatic steatosis based on data from diabetic rats despite the elevated circulated triglycerides (74). Lastly, a glucagon antagonist developed by Merck has been associated with increased LDL cholesterol and attributed to increased cholesterol absorption, as demonstrated in pre-clinical studies (75). The reduction in hepatic glucose output via these pathways show robust changes in glycemia, however, the impact on lipids should be of careful consideration.

THE EFFECT OF CIRCULATING LIPID-LOWERING DRUGS ON GLUCOSE AND LIPIDS

Niacin

Niacin, also known as nicotinic acid or vitamin B_3 has the ability to modify lipid abnormalities, by lowering LDL cholesterol and triglyceride while increasing HDL cholesterol (76). Niacin has been prescribed to patients with a high risk of CVD, such as atherosclerosis. Alternation of abnormal lipid species is mediated by indirect inhibition against VLDL formation (77). In particular, niacin down-regulates apolipoprotein B-100 production (78) and facilitates VLDL catabolism by activating LPL (79).

The effect of niacin in T2D has been controversial. With respect to glucose regulation, long-term treatment of nicotinic acid to treat CVD tends to increase the risk of T2D, because patients with impaired fasting glucose have shown elevated fasting blood glucose concentrations than normoglycemic groups (76). However, data from long-term clinical studies by Elam *et al*. report stable glucose homeostasis; although a slight increase in fasting blood glucose at the early stage of niacin treatment was observed (80). In conclusion, niacin has a positive effect on lipid regulation but does not have noticeable glucose lowering effect. The majority of clinical results do not mention any decrease in HbA1c and fasting blood glucose (76, 80).

Statins

Statins are prominent cholesterol lowering drugs, which inhibit HMG-CoA reductase, an enzyme that participates in the key step of cholesterol synthesis. The LDL cholesterol lowering effects of statins and cardiovascular benefits have been reported in many studies (81, 82). In addition, other potential benefits including effects on glucose metabolism have been suggested (83). Ogawa and colleagues demonstrated beneficial effects of pravastatin against impaired glucose tolerance (84). In particular, pravastatin treatment was shown to increase plasma adiponectin levels and significant association between elevated level of adiponectin and a decrease in blood glucose levels at the 2hr-post oral glucose tolerance test (OGTT) was observed (84). Despite these studies, conflicting results from other randomized statin trials implicated a slight increase in the risk of new-onset diabetes (85, 86). In conclusion, statin therapy against T2D has no positive effect, even though statin therapy markedly reduced lipid species, including LDL cholesterol.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor

PCSK9 inhibitor blocks the binding of PCSK9 to the LDL cholesterol receptor and induces lysosomal degradation. As a result, more LDL cholesterol receptors remain on the cellular membrane and become available to remove LDL cholesterol from the blood. Alirocumab, a PCSK9 inhibitor under development, has entered a phase III clinical trial (87) and exhibits significantly more effective LDL cholesterol lowering, compared to ezetimibe (88). However, there were no considerable changes in HbA1c or fasting blood glucose (88), which could translate to limited efficacy on controlling glucose concentrations by PCSK9 inhibitors.

Cholesteryl ester transfer protein (CETP) inhibitors

CETP mediates the transportation of the cholesteryl ester group of HDL cholesterol to VLDLs. This exchange induces a decrease in HDL cholesterol and increases VLDLs and LDL cholesterol, the main culprits of atherosclerosis (89). Based on the mechanism of CETP, synthetic inhibitors effectively block transfer of cholesteryl ester from HDL cholesterol to improve the lipid profile. Almost all clinical trials delineate similar results showing that CETP inhibitor monotherapy or combined therapies with statins are an effective means to raise anti-atherogenic HDL cholesterol (90, 91). In terms of T2D, further research is necessary. However, some studies, such as Barter *et al*., show positive effects of long-term treatment of torcetrapib and statins on glucose metabolism, resulting in decreased blood glucose, insulin, and HbA1c, as well as, cholesterol profile improvement (92).

THE EFFECT OF NOVEL METABOLIC DISEASE AGENTS ON LIPID AND GLUCOSE

Fibroblast growth factor 21 (FGF21)

FGF21 is a metabolic hormone with several beneficial effects on glucose and lipid metabolism and insulin sensitivity in pre-clinical trials. Most pre-clinical, *in vivo* results support the anti-diabetic effects of FGF21, demonstrating both lipid and obesity-induced hyperglycemia reductions (93). The key mechanism of action of FGF21 is through the adiponectin coupled metabolic response. Lin *et al*. demonstrated the role of adiponectin as an effector of FGF21 by using adiponectin knockout mice (94). Additionally, Bernardo *et al*. showed that functioning brown adipose tissue was not necessary for the favorable metabolic effects of FGF21 supporting the importance of white adipose tissue (95). Furthermore, translational clinical research using an FGF21 analogue treatment resulted in marked improvements of lipid abnormalities, including decreases in LDL cholesterol and triglycerides. Metabolically beneficial effects were also confirmed in terms of body weight and fasting insulin levels with a slight decrease in glucose (96). Positive data from pre-clinical and translational research indicates the potential of FGF21 as a new class of drug for metabolic

disorders, specifically in controlling dyslipidemia.

Apolipoprotein C3 (APOC3) inhibitors

APOC3 is one of the protein components of VLDLs and inhibits LPL (97). APOC3 inhibits hepatic uptake of triglyceride-rich lipoproteins by blocking the binding between apoB lipoproteins and their receptors (14). Genetic variants in APOC3 were discovered in Asian Indian men with high occurrence of NAFLD and insulin resistance (97). In Asian Indian individuals, as well as those of other ethnic groups, variants (C-482T, T-455C or both) in the insulin responsive element of the APOC3 gene, which can inhibit LPL and hepatic lipase, are associated with hypertriglyceridemia and hepatic steatosis (97). These polymorphisms are a gain of function mutation and lead to ~30% higher plasma APOC3 concentrations and post-prandial hypertriglyceridemia (97). This accounts for the high occurrence of NAFLD and insulin resistance in this ethnic group (98). The effect of increased plasma APOC3 concentrations on the development of NAFLD and hepatic insulin resistance has been genetically validated in transgenic mice that have increased hepatic overexpression of human APOC3 (99). These mice are more prone to diet-induced NAFLD and DAG–PKCε-induced hepatic insulin resistance (99). The development of hepatic lipid accumulation was due to decreased hepatic VLDL secretion by postprandial hyperinsulinemia. Interestingly, the insulin suppression of hepatic gluconeogenesis was diminished despite of hyperinsulinemia (99), indicating hepatic insulin resistance occurred selectively by the suppression of gluconeogenesis rather than VLDL suppression. Moreover, the loss-of-function mutation in APOC3 has been linked to favorable lipid profiles and lower incidences of coronary artery disease (100-102). More recently, a clinical trial showed remarkable improvements in familial chylomicronemia with inhibitors of APOC3 mRNA (103), suggesting a therapeutic potential of ApoC3 targeting against lipid-induced insulin resistance, NAFLD, dyslipidemia and CVD.

Monoacylglycerol/Diacylglycerol acyltransferase inhibitors

Diacylglycerol acyltransferase (DGAT) is an enzyme that catalyzes triglyceride synthesis from DAG. There are two key isoforms, DGAT1 and DGAT2. DGAT1 is critical in intestinal lipid absorption. DGAT2 appears to be critical for the secretion of VLDL triglycerides. Inhibition of DGAT1 is associated with adverse gastrointestinal side effects that limit the clinical utility of DGAT1 inhibitors. Novartis has tested the potential of using DGAT1 inhibitors in NASH and has observed reductions in hepatic fat content (AASLD poster #2147, http://www.aasld.org/events-professional-development/liver-meeting/scientific-program/poster4).

Several *in vivo* studies have demonstrated the importance of DGAT2 on hepatic lipid handling. Knocking down DGAT2 using an anti-sense oligonucleotide resulted in reduction of hepatic steatosis (104-106). In preclinical trials, DGAT2 inhibition has been shown to increase insulin responsiveness, as assessed by the hyperinsulinemiceuglycemic clamp technique (107). Subsequently, efficacy of DGAT1 inhibitors for human applications was tested and results showed noticeable regulation of lipid abnormalities (108, 109).

Similarly, monoacylglycerol acyltransferase (MGAT) enzymes, which convert monoacylglycerol to DAG, a key mediator of insulin resistance, have recently been considered of potential relevance to the mechanisms of obesity-related hepatic

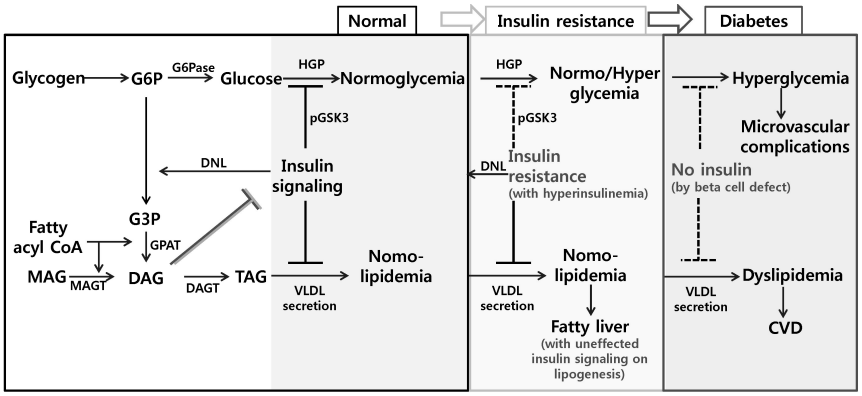

Fig. 1. A pathophysiological development of diabetes and associated co-morbidities. Concomitant with impaired insulin action on glucose metabolism and lipogenesis remains unaffected in the liver (25). Therefore, unsuppressed hepatic glucose production along with increased lipogenesis likely worsens the development of hepatic steatosis and dyslipidemia (16). This may partially explain why conventional anti-hyperglycemic agents have not shown benefits on the life-threatening macrovascular complications, including CVD atherosclerosis and coronary heart diseases. On the contrary, tissue lipid lowering diabetic drugs could have the potential to decrease both tissue and circulating lipid abnormalities, thereby partially linking diabetic dyslipidemia to increased CVD risk. HGP: hepatic glucose production, G6P: glucose-6-phosphate, DNL: de novo lipogenesis, DAG: diacylglycerol, TAG: triglyceride, VLDL: very low-density lipoprotein, MGAT: monoacylglycerol acyltransferase, DGAT: diglyceride acyltransferase.

steatosis (110-112). In the fatty liver of rodents (110, 111) and humans (112), MGAT gene expression increases. However, weight loss in obese subjects is associated with improved insulin sensitivity and hepatic steatosis decreases (112). In diet-induced obese mice, inhibition of MGAT acts to cause a degree of lipid-induced hepatic insulin resistance, which can lead to hyperglycemia, as well as, diabetic dyslipidemia that is closely linked to CVD (Fig. 1). Thus, anti-diabetic drugs, which modulate tissue lipids, may be considered as a strategy to treat the underlying NAFLD, hepatic insulin resistance, and modify CVD risk.

CONCLUSION

In metabolism, glucose and lipids are highly interrelated. Affecting lipid or glucose metabolism can cause the flux of carbon to divert into an alternate pathway. Careful attention to the impact of pharmacological agents for T2D on lipids and conversely the impact of agents to control lipids on glycemic control should be made. Since metabolic diseases often include both adverse changes in lipids and glucose, future research should be directed to therapeutic strategies that treat the underlying pathophysiology of metabolic diseases to reduce both glucose and lipid concentrations.

ACKNOWLEDGEMENTS

We thank Thanh Erion, PhD for the careful input and review of this manuscript. Due to space limitation, this review cites only a limited number of studies that have been performed on the pharmacological agents described and does not contain a full list of citations to other studies that have been performed on these pharmacological agents. This work was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2014R1A1A1002009 and NRF-2014M3A9D5A01073886).

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