

Refocusing Peroxisome Proliferator Activated Receptor- α : A New Insight for Therapeutic Roles in Diabetes

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Although glucose-lowering treatment shows some risk lowering effects in cardiovascular diseases, risks of macrovascular and microvascular complications have still remained, and development of new therapeutic strategies is needed. Recent data have shown that peroxisome proliferator activated receptor- α (PPAR- α) plays a pivotal role in the regulation of lipid homeostasis, fatty acid oxidation, cellular differentiation, and immune response such as inflammation or vascularization related to diabetic complication. This review will re-examine the metabolic role of PPAR- α , summarize data from clinical studies on the effect of PPAR- α agonist in diabetes, and will discuss the possible therapeutic role of PPAR- α activation.

Keywords: Diabetes; Diabetes complications; Fibric acids; Peroxisome proliferator activated receptor agonists

INTRODUCTION

The global prevalence of type 2 diabetes (T2D) is rapidly increasing, and considerable population suffers from diabetes-related complication [1]. T2D is closely associated with an increased risk of macrovascular and microvascular risk [2,3]. The most important aim of treatment of T2D is lowering macrovascular and microvascular risk. There have been efforts to reduce the residual risk of macrovascular and microvascular complication, and many previous clinical trials showed meaningful risk reduction of cardiovascular risk after multifactorial risk factor modifications [4-7]. However, the residual risk still remained after achieving targets for glucose, blood pressure, and low density lipoprotein (LDL) levels [8].

Focuses on activation of peroxisome proliferator activated receptors- α (PPAR- α) have been made for risk reduction of diabetic complications; however, its therapeutic role in diabetes is still controversial. With this background, we will discuss

the actions of PPAR- α agonists and clinical implications for the preventions of macrovascular and microvascular complications in T2D.

PPAR AGONIST

PPARs

PPARs are a subgroup in the family of nuclear hormone receptors and are highly expressed across numerous metabolic tissues [9]. PPARs are activated by binding ligands, including fatty acids, in the cytoplasm and are then translocated to the cell nucleus.

In the nucleus, PPARs form heterodimers with retinoic acid receptors (RXR) [10-12]. The generally conserved domain structures are found in PPARs and RXRs: DNA-binding domains, ligand-binding domains, and activation domains. DNA-binding domains make the receptor bind to PPAR and RXR response elements in target gene promoters. Ligand-binding do-

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mains determine how specific pharmacologic and endogenous nuclear receptor ligands bind to and modulate receptor activity. Activation domains determine receptor activities [9].

PPARs can be influenced by variable factors and shows variable responses by clinical agonists [13]. Because DNA-binding domains are relatively large, many PPAR-agonists can attach to the ligand-binding domain in a distinctive pathway, which results in specific conformational changes and different accessory molecule recruitment. One of the reasons of unique effect of a PPAR agonist on different tissues is partially due to the variety of accessory molecules in the specific tissues. The formation of endogenous ligands or the catabolism of synthetic agonists may also vary, which may result in a wide range of responses. PPARs also can be modified by phosphorylation, and variable factors of RXR could influence on PPAR response [9].

By binding to the promoter regions of target genes, PPARs become transcription factors which regulate the expression of multiple target genes. Activation of PPARs pathways are known to result in favorable effects on glucose homeostasis and lipid metabolism [14,15]. There are three PPAR isotypes: PPAR- α , PPAR- γ , and PPAR- δ (also referred to PPAR- β).

PPAR- α agonist

PPAR- α was the first discovered PPARs and is known to promote proliferation of peroxisomes, which is involved in oxidative processes including fatty acid metabolism and inflammatory and vascular pathways [9]. PPAR- α is highly expressed in skeletal muscles and liver, which is closely correlated with fatty acid oxidation [16,17]. The primary mechanism of action of PPAR- α is increasing lipoprotein lipase activity which hydrolyzes triglyceride-rich lipoproteins, and reducing its inhibition; PPAR- α activation represses the expression of apolipoprotein (Apo) C3, which is the endogenous lipoprotein lipase repressor [9,17]. PPAR- α activation also increases the expression of fatty acid repressors such as CD36, and increases production of various enzymes correlated to β -oxidation. Activation of PPAR- α also increases levels of Apo A-I and high density lipoprotein cholesterol (HDL-C) and up-regulates cellular transporters involved in the cholesterol efflux pathway. As a result, PPAR- α activation results in increased HDL-C level, stimulates reverse cholesterol transport, and lowers triglyceride level [18,19]. In clinical practice, PPAR- α agonists (fibrates) are used for dyslipidemia by decreasing triglyceride levels and increasing HDL levels [14].

PPAR- γ agonist

PPAR- γ is highly expressed in adipocytes, skeletal muscle, liver, and kidney. PPAR- γ has been known to regulate expression of genes that mediate general energy metabolism, such as adipocyte differentiation and insulin action [15]. PPAR- γ is correlated with increasing insulin sensitivity and glucose uptake, adiponectin, and fatty acid uptake [9,20]. Therefore, selective PPAR- γ agonists (thiazolidinediones) had been widely used in clinical practice to treat T2D [21]. However, the use of thiazolidinediones requires caution because some had shown several undesirable side effects, such as water retention, peripheral edema, and congestive heart failure, osteoporosis, and while still under controversy, possible increased risk of bladder cancer [22-24].

PPAR- β/δ agonist

PPAR- β/δ can be found in almost all cell types and tissues, which suggests their crucial role across the whole body [25]. Previous *in vivo* data have shown that selective overexpression of PPAR- β/δ in mouse adipose tissue induces significant weight loss and provides protection against obesity and dyslipidemia after high fat diet [26]. The metabolic effects of PPAR- β/δ are correlated with increased fatty acid oxidation, energy consumption, and adaptive thermogenesis. Although PPAR- β/δ agonists are not currently used in clinical practice, some clinical studies on pan-PPAR agonist, including bezafibrate, show potentially favorable metabolic benefits of pan-PPAR agonist that includes PPAR- β/δ activation, especially in offsetting weight gain issues of selective PPAR- γ agonist [25,27].

THE THERAPEUTIC POTENTIAL OF PPAR- α AGONIST IN DIABETES

PPAR- α agonist in macrovascular complications

There are two major clinical studies about the effects of fenofibrates on cardiovascular complication. One is the Fenofibrate Intervention and Event Lowering in Diabetes Study (FIELD), which included 9,795 subjects with diabetes mellitus and dyslipidemia [28,29]. In this study, fenofibrate did not reduce the composite primary end point of nonfatal myocardial infarction and coronary heart disease mortality (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.75 to 1.05) compared with placebo. Fenofibrate showed significantly reduced nonfatal myocardial infarction (HR, 0.79; 95% CI, 0.62 to 0.94), with nonsignificantly increased mortality in coronary heart disease

(HR, 1.19; 95% CI, 0.90 to 1.57). Fenofibrate showed significantly reduced composite end point of cardiovascular disease mortality, myocardial infarction, stroke, and coronary or carotid revascularization (HR, 0.89; 95% CI, 0.80 to 0.99). In post hoc analysis, fenofibrate reduced 5-year composite risk of myocardial infarction, stroke, and death in subjects with metabolic syndrome (adjusted HR, 0.89; 95% CI, 0.79 to 1.00) or without (adjusted HR, 0.88; 95% CI, 0.62 to 1.19). Subjects with metabolic syndrome had higher baseline risk, which may explain the greater absolute benefits in those subjects [30].

The other study is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which included 5,518 subjects with diabetes mellitus, with hemoglobin A1c (HbA1c) greater than 7.5%, and elevated cardiovascular disease risk factors [5,31]. They were randomized to masked fenofibrate or placebo, each on a background of open-label simvastatin. After a mean follow-up period of 4.7 years, the annual primary outcome (the first occurrence of a major cardiovascular event including nonfatal myocardial infarction, stroke, or cardiovascular death) rate was 2.2% in fenofibrate group and 2.4% in placebo group (HR, 0.92; 95% CI, 0.79 to 1.08). Fenofibrate did not show a significant reduction in nonfatal myocardial infarction and cardiovascular mortality [5]. They concluded that this combination of lipid treatment does not improve cardiovascular outcomes.

The effects of gemfibrozil on cardiovascular complications were also examined by two large trials. The Helsinki Heart Study included 4,180 men aged 40 to 55 years with primary dyslipidemia (defined as non-HDL-C level >5.2 mmol/L) [32]. Within 1 year after being randomized to either gemfibrozil or placebo, HDL-C and LDL-cholesterol (LDL-C) improved in the former group by 10%, whereas minimal changes were observed in the latter group. Compared to placebo group, gemfibrozil group showed lower events of fatal or nonfatal myocardial infarction (relative risk reduction [RRR], 34%; 95% CI, 8.2 to 52.6) at 5-year follow-up.

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial also showed similar results. In this study, 2,531 men with cardiovascular disease, HDL-C level <1.0 mmol/dL, and LDL-C level 3.6 mmol/dL were randomized to gemfibrozil or placebo [33]. After 5 years, gemfibrozil reduced primary composite end point of combined incidence of nonfatal myocardial infarction (RRR, 23%; 95% CI, 4 to 38) or cardiac death (RRR, 22%; 95% CI, 2 to 41). These trials showed that gemfibrozil may reduce the risk of myocardial infarction and

cardiac death in high risk patients.

PPAR- α agonist in microvascular complications

Activation of PPAR- α results in inhibition of several mediators of vascular damage, including inflammation, endothelial dysfunction, lipotoxicity, and thrombosis [34,35]. In addition, fenofibrate showed an effect on decreasing uric acid [36,37]. Due to these effects, activation of PPAR- α has been suggested to possibly affect the prevention of diabetic nephropathy or retinopathy [34,35,38-40].

Diabetic nephropathy is one of the most important causes of chronic kidney disease. Recent studies suggest that lipotoxicity by lipid accumulation in kidney is one of risk factors for diabetic nephropathy [39,41,42]. Dyslipidemia, oxidative stress, and inflammation closely correlated with renal dysfunction. Therefore, PPAR- α could have a therapeutic role in diabetic nephropathy, which is being supported by increasing amount of evidence [43,44]. In a previously reported *in vitro* study, after treatment of human glomerular microvascular endothelial cells with fenofibrate, transient activation of adenosine monophosphate-activated protein kinase, induction of the phosphorylation of protein kinase B, eNOS activation, and nitric oxide production occurred [35]. Another *in vivo* study reported that fenofibrate treatment in diabetic rat prevented the development of diabetes-induced lipid elevation, vascular endothelial dysfunction, and oxidative stress. In this study, fenofibrate prevented the induction of diabetic nephropathy by reducing proteinuria and blood urea nitrogen [43]. Unfortunately, few clinical studies have confirmed renoprotective effect of PPAR- α activation in diabetic nephropathy. In the FIELD study, fenofibrate reduced albuminuria (albumin/creatinine ratio by 24% vs. 11%; $P < 0.001$) and slowed estimated glomerular filtration rate loss over 5 years compared with placebo [45]. The investigators of this trial suggested that fenofibrate could have a protective role against the loss of underlying renal function in T2D. In FIELD Study, plasma creatinine was noted to be increased during fenofibrate therapy, but was quickly reversed after placebo assignment. Other study suggested that fenofibrate-induced increase in creatinine production was associated with enhanced metabolic production rate of creatinine, rather than with impairment of renal function [46].

The Diabetes Atherosclerosis Intervention Study included subjects with T2D treated with fenofibrate for an average of 38 months. This study suggested that fenofibrate reduced progression of normal albumin excretion to microalbuminuria [47].

Other PPAR- α agonist such as gemfibrozil and bezafibrate also showed reno-protective effect in diabetic nephropathy [48,49].

The effect of PPAR- α activation on diabetic retinopathy was examined in the FIELD study. The FIELD study showed fenofibrate reduced the need for laser photocoagulation for either macular edema or proliferative retinopathy compared to placebo (3.4% vs. 4.9%; $P < 0.001$) [50]. The ACCORD Eye study showed similar results: intensive treatment of dyslipidemia (160 mg fenofibrate daily plus simvastatin or placebo plus simvastatin) resulted in reduced progression rates of diabetic retinopathy [51].

DEVELOPMENT OF THE DUAL PPAR- α/γ AGONIST

Both PPAR- α and PPAR- γ agonist plays a pivotal role in treatment of T2D. PPAR- α activation improves lipid profile, including reduction of triglyceride levels and enhancement of HDL-C levels. PPAR- γ activation enhances insulin sensitivity and potential anti-inflammatory effects. For these reasons, interests in dual PPAR- α/γ agonist have been sparked among a number of researchers. However, the development of dual-PPAR agonist has not been steady due to safety concerns.

Tesaglitazar was the first dual PPAR- α/γ agonist with relatively weak potential, but nephrotoxicity was found, and consequently, the development was discontinued [52,53]. The use of ragaglitazar and naveglitazar was correlated with increased incidence of bladder cancer and hyperplasia in rodent studies [54,55]. Muraglitazar showed significant lipid changes, with decreases in triglyceride by up to 27% and increases in HDL-C by up to 16%. Despite of these effect, further studies on mura-
glitazar was also discontinued due to increases in the composite risk of nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality compared with placebo or pioglitazone in meta-analysis (relative risk, 2.23; 95% CI, 1.07 to 4.66) [56,57].

Aleglitazar is another dual PPAR- α/γ agonist and equally stimulates PPAR- α and PPAR- γ genes [58]. In the phase II Effect of the Dual Peroxisome Proliferator-Activated Receptor- α/γ Agonist Aleglitazar on Risk of Cardiovascular Disease in Patients With Type 2 Diabetes (SYNCHRONY) study, aleglitazar showed dose-dependent metabolic benefits, including significant dose-dependent reduction in HbA1c of -0.36% (4 mmol/mol, 50 μ g; $P = 0.048$) to -1.35% (15 mmol/mol, 600 μ g; $P < 0.0001$) in 16 weeks of treatment compared to placebo. Aleglitazar also showed significant beneficial effects on lipid profile:

significant decreases in triglyceride and increases in HDL-C were found (-43% and +21%, respectively, with 150 μ g). At a dose of 150 μ g or higher, aleglitazar also significantly decreased LDL-C (placebo-adjusted reduction rate -15.5% with 150 μ g) compared to placebo. The effects of 150 μ g of aleglitazar on triglycerides, HDL-C, and LDL-C were greater than 45 mg of pioglitazone. Further study has found treatment of aleglitazar to result in a shift from the atherogenic small dense LDL particles associated with T2D to larger LDL particles [59]. Reported adverse events with aleglitazar were similar to pioglitazone, with mild increases body weight and edema. However, no serious adverse events such as cardiovascular disease or hepatotoxicity have been confirmed as of yet, with the exception of a reversible small decline in glomerular filtration rate [60]. The phase III Cardiovascular Outcomes Study to Evaluate the Potential of Aleglitazar to Reduce Cardiovascular Risk in Patients With a Recent Acute Coronary Syndrome (ACS) Event and Type 2 Diabetes Mellitus (ALECARDIO) study is now ongoing; this randomized controlled clinical trial will examine whether aleglitazar (150 μ g daily dose) can decrease cardiovascular morbidity and mortality in T2D patients who have suffered from a recent acute coronary syndrome event (NCT01042769).

CONCLUSIONS

Although modification of multiple risk factors of microvascular and macrovascular complication of T2D has resulted in risk reduction, the concern for remaining risk has been continuously raised, and further reducing this remaining risk has been the main therapeutic issues in T2D.

Activation of PPAR- α has been suggested as an important therapeutic target for patients with T2D through playing an important role in regulation of energy metabolism. Further research is required to determine whether PPAR- α agonist shows actual risk reduction for microvascular complication. Furthermore, the development of dual PPAR- α/γ agonist has been of great interest because of its mechanism which may potentially provide benefits on both lipid profile and glycemic control. The effect of dual PPAR- α/γ agonist on glycemic control, lipid profile, cardiovascular outcomes, and safety issues also should be verified with further studies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was re-

ported.

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