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REVIEW

Anti-Diabetic Effect of Telmisartan Through its Partial PPARγ-Agonistic Activity

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Abstract: Telmisartan is an angiotensin II receptor antagonist, which selectively inhibits the angiotensin II type 1 receptor. Thus, it is widely used for hypertension management. Nowadays, telmisartan's effect on peroxisome proliferator-activated receptors (PPARs) is gaining wider attention. PPARs are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily. Telmisartan is reported to have a partial PPARγ-agonistic effect while avoiding the safety concerns found with full PPARγ agonists (thiazolidinediones). Telmisartan could be an alternative treatment option, with dual benefit for diabetes mellitus (DM) and hypertension. This review summarizes the anti-diabetic activity of telmisartan via its partial PPARγ-agonistic activity.

Keywords: diabetes mellitus, hypertension, peroxisome proliferator-activated receptors, telmisartan

Introduction

Telmisartan

Telmisartan is a selective angiotensin II type 1 receptor antagonist (angiotensin receptor blocker [ARB]) which does not affect the other receptor systems involved in cardiovascular regulation.[1,2] It is a more lipophilic compound than other ARBs, which facilitates oral absorption and benefits tissue and cell penetration.[3] The drug is used for the management of hypertension, either as monotherapy or as combination therapy with other antihypertensive agents.[1,4] It is considered as a first-line drug in mild-to-moderate hypertension with an excellent safety profile, and is used for the treatment of hypertension-related cardiovascular end-organ damage.[5] A number of studies have shown that telmisartan has partial PPARγ-agonist activity, activating 25–30% of the receptor compared to the full PPARγ agonists.[6–8]

Peroxisome Proliferator-Activated Receptors (PPARs)

PPARs are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily.[9] PPARs comprise three subtypes, namely PPARα, PPARγ, and PPARβ/δ.[10]

Among the three subtypes, PPARγ is the most studied nuclear receptor and is involved in the control of energy balance, glucose and lipid homeostasis.[11] Thiazolidinediones, including rosiglitazone and pioglitazone, are anti-diabetic drugs acting on PPARγ.[12] Thiazolidinediones promote insulin sensitization and improve dyslipidemia in diabetic patients.[13] It has been reported that PPARγ agonists may have various therapeutic advantages in addition to anti-diabetic activity. Rosiglitazone decreased arterial stiffness and clinical inflammatory responses in diabetic patients with coronary artery disease.[14,15]

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Despite the beneficial effects of thiazolidinediones on the heart, they are also associated with several adverse effects, including cardiac dysfunction and ventricular fibrillation.[16,17]

Challenges with Full-PPARγ Agonists

Full PPARγ agonists are associated with a number of side effects, including weight gain, fluid retention (edema), and cardiac toxicity.[18] The first approved drug from the thiazolidinedione class was troglitazone, which was withdrawn from the market in 2000 owing to its fatal hepatotoxicity.[19] This idiosyncratic hepatotoxicity is mediated through oxidative stress and involves mitochondrial dysfunction.[20,21] Other thiazolidinediones are also associated with adverse effects, including weight gain (adiposity), increased rate of bone fracture, anemia, and hepatic damage.[22]

Rosiglitazone is associated with granulomatous hepatitis.[23,24] It has also been reported to increase cardiovascular risk.[25] Hypertension, myocardial ischemia, heart failure, upper respiratory tract infection, and diarrhea were also reported with rosiglitazone use.[26] Owing to its cardiovascular side effects and adverse effects on the lipid profile, rosiglitazone was banned in India in 2010.[27]

Clinical use of pioglitazone is also limited by undesirable adverse effects, including weight gain, precipitation of heart failure, peripheral edema, and an increase in bone fractures.[28,29] Pioglitazone is also reported to induce hepatic damage.[30,31] Although the severity depends on the dose administered, subchronic administration of pioglitazone in mice resulted in nephrotoxicity, hepatotoxicity, cardiotoxicity, and hematological disorders, which were supported by biochemical abnormalities and histopathological changes.[32] For this reason, new PPARγ ligands with increased therapeutic efficacy and reduced adverse effects are needed. Partial PPARγ modulators are one of the promising classes in this regard.[33]

Advantages of Partial PPARγ Agonists

PPARγ partial agonists selectively modify the expression of genes needed only for insulin sensitization without activating the genes responsible for weight gain and edema.[34] This makes partial PPARγ agonists preferable to full agonists.[35] Adverse effects including weight gain and edema may lead to heart failure, and other adverse effects may also be avoided by selective modulation of the PPARγ receptor.[36]

The partial PPARγ agonist balaglitazone showed fewer untoward effects, including fluid and fat accumulation, compared to the full PPARγ agonist pioglitazone.[37] Another selective partial activator of PPARγ (PAR-1622) showed anti-diabetic activity with a broader safety margin against fluid retention in comparison with rosiglitazone.[38] PAM-1616 is also a selective modulator of PPARγ with anti-hyperglycemic properties and an improved side effect profile compared to rosiglitazone.[39] KR-62980 is a selective PPARγ modulator with anti-diabetic and anti-adipogenic activity with an improved side effect profile.[40,41] CMHX008, a partial PPARγ modulator, showed comparable insulin-sensitizing effects with lower adipogenic capacity and lower risk of bone loss compared to rosiglitazone, and it could be an effective agent for the management of DM and other metabolic disorders.[42,43] GQ-16 and L312, PPARγ partial agonists, also showed a promising anti-diabetic effect with an improved side effect profile.[44,45] There are several partial PPARγ agonists under investigation, with an insulin sensitization action and fewer adverse effects, including a reduced tendency to cause weight gain, adipose tissue gain, and fluid retention.[46]

PPARγ partial activation may have an important endothelial defensive action through activating eNOS, generating nitric oxide (NO) and enhancing NO bioavailability, reducing oxidative stress, and preventing the adhesion cascade and vascular inflammation.[47] Partial PPARγ agonists may offer beneficial effects for the management of type II DM (T2DM) with attenuated adverse effects such as fluid retention and cardiac hypertrophy.[34]

Patients with hypertension and T2DM may obtain a dual benefit from drugs such as telmisartan with multiple targets (AT1R and PPARγ). That would potentially reduce the pill burden and side effects of multiple medication use, and hence improve medication adherence. This review focuses on the anti-diabetic effects of telmisartan mediated through PPARγ.

Telmisartan for Diabetes Mellitus

Current management of DM is associated with major hurdles, comprising polypharmacy, striving for glycemic targets, patient adherence, and clinical inertia.[48] In spite of many anti-diabetic drugs being available, adequate control of diabetic hyperglycemia often remains difficult to achieve.[49] In T2DM, intense control of glycemia generally requires the addition of insulin to oral agents, which is consistently accompanied by weight gain. Furthermore, increased hypoglycemia carries a risk of cerebral damage, mental disorders and stroke, cognitive damage,

hypertension, and renal disease.[50] The adverse effects associated with currently available drugs include GI adverse effects and lactic acidosis with metformin,[51,52] weight gain and hypoglycemia with sulfonylureas, and fluid retention and weight gain with thiazolidinediones.[53] Since the available agents are associated with various adverse effects, it is important to discover an alternative agent that is more effective and safer to use in the treatment of T2DM.[53,54]

As telmisartan is reported to have partial PPARγ-agonistic effect, the drug can regulate glucose and lipid metabolism, and improve insulin resistance.[55] PPARγ phosphorylation and its downstream gene expression may be regulated by telmisartan, promoting glucose uptake and acting as an insulin-sensitizing agent in adipocytes.[56] Telmisartan augments glucose transporter-4 protein expression and 2-deoxyglucose uptake in the basal and insulin-stimulated states of adipocytes.[57] It further increases glucose transporter-4 localization to the plasma membrane and enhances glucose uptake through PPARγ in adipocytes. Thus, telmisartan could be an effective therapy for metabolic syndrome.[58]

Different mechanisms have been postulated for the glucose-lowering potential of telmisartan. It may occur through the suppression of reactive oxygen species and an agonistic effect on PPARγ.[59] Telmisartan decreased malondialdehyde and increased glutathione, catalase, and superoxide dismutase levels in STZ-induced type 2 diabetic rats, and prevented cardiovascular complications.[60] Furthermore, telmisartan was shown to increase serum adiponectin and improved both oxidative stress and insulin resistance in type 2 diabetic patients.[61] Also, in diabetic patients with hypertension, telmisartan increased high-molecular-weight adiponectin levels and improved insulin resistance, through partial PPARγ activation.[62] Adiponectin, through binding to its receptors, mediates the insulin-sensitizing effect, which is important in DM patients.[63]

In addition, interruption of the renin–angiotensin–aldosterone system (RAAS) may improve glycemic control in T2DM, since the RAAS is implicated in the development of T2DM.[64] Owing to the ability of telmisartan, partial activation of PPARγ and ARB blockade may have additional importance not merely in the management of metabolic syndrome and prevention of T2DM but also in the prevention and treatment of atherosclerotic cardiovascular disease.[65]

Telmisartan improves insulin sensitivity in hypertensive patients with insulin resistance or T2DM.[66] Telmisartan treatment of hypertensive patients with T2DM not only improved blood pressure, glucose and lipid metabolism, but also improved endothelial function for the prevention of atherosclerosis.[67] Through activating PPARγ, telmisartan reduces cardiac fibrosis and hypertrophy, thus preventing unfavorable cardiac remodeling.[7] In addition to PPARγ activation, telmisartan improves hyperglycemia-induced cardiac fibrosis through PPARδ activation.[68,69] Telmisartan may be important in preventing diabetic cardiomyopathy and it could be used to treat both hemodynamic and metabolic aberrations.[70,71] These cardioprotective effects of telmisartan may be due to improvement of endothelial function, which is associated with PPARγ-eNOS, oxidative stress, and the Rho-kinase pathway.[72] Targeting both angiotensin type 1 receptor and PPARγ may be important in treating hyperlipidemia, insulin resistance, hypertension, and stroke, and ultimately mitigating the burden of cerebrovascular and cardiovascular disease.[73]

Patients with uncomplicated hypertension and mild dyslipidemia can be effectively treated with telmisartan.[74] Both animal and human studies showed improvements in the lipid profile with telmisartan treatment. In high-fat diet-induced dyslipidemic guinea pigs, telmisartan markedly decreased triglyceride and slightly increased high-density lipoprotein cholesterol levels.[75] In a prospective open-label study, telmisartan significantly increased high-density lipoprotein and decreased triglyceride and total cholesterol in hypertensive patients with dyslipidemia.[76] Telmisartan may have hepatic partial PPARα agonist activity and it increases lipoprotein lipase expression via a PPARα-dependent pathway, which could explain telmisartan's anti-dyslipidemic actions.[77,78]

Telmisartan has the additional benefit of renoprotection in patients diagnosed with diabetes and hypertension. In a randomized, multicenter, double-blind, placebo-controlled trial, telmisartan reduced the transition from incipient to overt nephropathy and induced remission of albuminuria in Japanese patients with T2DM; telmisartan achieved superior renoprotection.[79] In addition, in a multicenter, prospective, double-blind, forced-titration, randomized study, telmisartan and ramipril both increased nitric oxide activity of the renal endothelium significantly, which in turn may support the preservation of cardiovascular and renal function in patients with T2DM.[80]

A number of preclinical and clinical studies have shown a decrease in blood glucose and improvement in diabetic complications after treatment with telmisartan (Table 1).

Table 1 Effects of Telmisartan in Diabetes Mellitus and Associated Complications

Reference	Study Design	Model	Method and Intervention	Major Outcome(s)
81	Experimental study	Streptozotocin (STZ)-induced DM in Wistar rats	DM was induced by the administration of STZ. Animals were administered with telmisartan for 28 days	Capillary blood glucose level was lower at all intervals Telmisartan improved the lipid profile. Hypoglycemic activity and improved lipid profile were comparable with glibenclamide
82	Experimental study	STZ-induced DM in rats	Diabetic rats were treated with/without telmisartan for 2 weeks	Telmisartan decreased SGLT2 expression in the PCT Insulin resistance was ameliorated in diabetic rats
[83	Experimental study	STZ-induced DM in rats	Diabetic rats were challenged with nicotinamide to induce diabetic nephropathy	The addition of telmisartan to vildagliptin demonstrated the best control over blood pressure, glycemia, and diabetic nephropathy markers, renal structural changes, and improvement of renal function
84	Experimental study	STZ-induced diabetic nephropathy in rats	After grouping, rats were treated with telmisartan (10 mg/kg), ramipril (5 mg/kg), or vehicle for 16 weeks	Telmisartan pretreatment reduced blood glucose level after 8 weeks Telmisartan significantly altered other parameters towards normal levels
85	Experimental study	HFFD + STZ-induced diabetes and insulin resistant	Animals were treated with telmisartan and/or metformin	Addition of telmisartan to metformin successfully restored serum glucose back to normal levels and improved serum total cholesterol (TC), triglycerides (TG), and adiponectin
86	Experimental study	STZ-induced DM	Diabetic rats were treated with telmisartan or gliclazide	Telmisartan or gliclazide produced beneficial effects on serum glucose, Hb, and HbA_{1c}. Restored tissue GSH and SOD with a fall in tissue thiobarbituric acid reactive substances
87	Clinical study	Five-year, double-blind, double-dummy, randomized study	250 patients with hypertension and early type 2 diabetic nephropathy were included to compare the effect of telmisartan with enalapril	Telmisartan was not inferior to enalapril in reducing the decline in GFR None of the patients developed serum creatinine >200 μmol/L, and none of them required dialysis
88	Clinical study	Randomized controlled trial	3488 adults at high risk for CVD, but free from diabetes, were involved	21.8% of participants treated with telmisartan and 22.4% of those on placebo developed diabetes Participants originally diagnosed with IFG and/or IGT were equally likely to regress to normoglycemia (26.9% vs 24.5%)

(*Continued*)

Table 1 (Continued).

Reference	Study Design	Model	Method and Intervention	Major Outcome(s)
89	Clinical study	Homeostatic model assessment–insulin resistance (HOMA-IR) in hypertensive subjects with MS	42 patients were involved in the study. Cytokines and metabolic parameters were analyzed before and after treatment with telmisartan	Treatment with telmisartan diminished 35% of HOMA-IR Telmisartan had more favorable effects on glucose homeostasis in patients with MS and low levels of serum cytokines
90	Clinical study	Randomized, parallel-group, open-label, crossover, prospective study	Patients were on 20 mg of lisinopril or 80 mg of telmisartan once a day for 24 weeks. Then, patients were randomized to continuing treatment with the respective monotherapy or with lisinopril plus telmisartan for a further 28 weeks	Dual blockade may provide a new approach to prevention of diabetic nephropathy in patients with type 2 diabetes, hypertension, and microalbuminuria
91	Clinical study	Randomized, placebo-controlled, double-blind, crossover study	20 volunteers with insulin resistance and abdominal overweight were involved	Compared to placebo, telmisartan resulted in a reduction in glucose area under the curve during intravenous glucose tolerance There was an increase in the insulinogenic index, indicating improved beta-cell function
92	Clinical study	Non-comparative, open-label study	34 patients with diabetic nephropathy were involved. Telmisartan (40 mg) was added to ACEI treatment and the patients were observed for 12 weeks	The addition of telmisartan resulted in a significant reduction in albuminuria
93	Clinical study	Randomized, placebo-controlled, double-blind, multicenter study	Patients with type 2 diabetes and incipient nephropathy were involved. Normotensive type 2 diabetic patients treated with telmisartan or placebo over 52 weeks	Patients treated with telmisartan showed lower transition rates from microalbuminuria to overt nephropathy In addition, more patients on telmisartan reverted to normoalbuminuria. Telmisartan prevented the progression of microalbuminuria in normotensive patients with type 2 diabetes
94	Clinical study	Randomized controlled comparative trial	82 individuals with DM and HTN were involved. They were on telmisartan or lisinopril or placebo control for 1 month	Significant improvement in both serum malondialdehyde (MDA) and total antioxidants status (TAS) parameters. Both lisinopril and telmisartan were able to subside oxidative stress in diabetic hypertensive patients
95	Clinical study	Double-blind, parallel-group, randomized study	Patients were treated with once-daily doses of telmisartan or losartan for 3 months	Telmisartan significantly reduced free plasma glucose, free plasma insulin, HOMA-IR, and HbA_{1c}. Plasma glucose and insulin were reduced during the oral glucose tolerance test by telmisartan

(*Continued*)

Table 1 (Continued).

Reference	Study Design	Model	Method and Intervention	Major Outcome(s)
96	Clinical trial	Double-blind, parallel-group, randomized study	65 overweight and obese patients with mild to moderate hypertension were involved. Patients were randomized to telmisartan or olmesartan for 3 months	Telmisartan improved blood pressure, glucose, insulin, HOMA-IR, and leptin in hypertensive diabetic patients

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; GSH, glutathione; Hb, hemoglobin; HbA_{1c}, hemoglobin A_{1c}; HFFD, high-fat, high-fructose diet; HOMA-IR, homeostatic model assessment–insulin resistance; HTN, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MS, metabolic syndrome; PCT, proximal convoluted tubule; SGLT2, sodium–glucose co-transporter-2; SOD, superoxide dismutase; STZ, streptozotocin; TC, total cholesterol; TG, triglyceride.

Conclusion

Telmisartan is a well-known anti-hypertensive drug, which is currently in clinical use. The partial PPARγ-agonistic activity and angiotensin receptor blockade activity of telmisartan have been shown to have multiple clinical benefits, including anti-diabetic and cardiovascular effects. In addition, telmisartan is reported to have PPARα and PPARδ agonist activity. Telmisartan would be an ideal alternative dual-purpose medication for patients with T2DM, hypertension and other cardiovascular disorders. However, this requires further detailed understanding of the therapeutic efficacy and molecular mechanism of telmisartan and other partial PPARγ-agonist drugs.

Abbreviations

ARB, angiotensin receptor blocker; DM, diabetes mellitus; GC, glibenclamide; GSH, glutathione; HbA_{1c}, hemoglobin A_{1c}; HOMA-IR, homeostatic model assessment–insulin resistance; MDA, malondialdehyde; PCT, proximal convoluted tubule; RAAS, renin–angiotensin–aldosterone system; SOD, superoxide dismutase; STZ, streptozotocin; T2DM, type 2 diabetes mellitus; TAS, total antioxidant status.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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