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Review Article

Peroxisome proliferator-activated receptors and thiazolidinediones in diabetic nephropathy

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ABSTRACT

Diabetic nephropathy is global problem with several drugs into trial without much success the current article highlights the role of thiazolidinedione's in diabetic nephropathy by scrutinizing and reconnoitring the cellular and intracellular mechanism and shielding action and the role of peroxisome proliferator-activated gamma receptors (PPARγ) receptors. Not only anti-diabetic action but renal protective effect with evidence based study has been highlighted. PPAR γ-is versatile target having numerous benefits and mainly preventing fibrosis in diabetic experimental model and some clinical case report yet, the benefits are not up to mark, since renal failure itself causes volume expansion and the thiazolidinedione's (TZDs) also preserve salt and water and lead to congestive heart failure which constraints its clinical application. Dual activators and balaglitazone selective PPAR modulator are having upcoming potential for treatment of diabetic nephropathy. Further detail investigation on such drug is needed to explore. However adverse effect like heart failure, osteoporosis and volume expansion effect over-rides the beneficial effect thus limiting its clinical use of currently available TZDs.

Keywords: Thiazolidinediones, Diabetic nephropathy, PPARγ

INTRODUCTION

In diabetes kidney changes are characterized by slowly advancing inflammation and fibrosis, leading to diabetic nephropathy (DN) and deteriorating renal function. A number of innovative treatments have also been verified in the investigational diabetic model and humans together with exercise, inhibitors of the renin-angiotensin system (RAAS) (angiotensin type 1 receptor blockers, angiotensin-converting enzyme inhibitors), inhibitors of advanced glycation end products (AGEs) like pyridoxamine, peroxisome proliferator- activated receptor PPAR new drug targets like histone deacetylase inhibitors which are still in embryonic stage, fibroblast activation protein inhibitors, nicotinamide adenine dinucleotide phosphate oxidase inhibitors and transforming growth factor beta 1 signalling as novel target for treatment of DN and various other molecular drug target are highlighted.[1-5]

Family of nuclear receptors entitled peroxisome proliferator-activated receptors (PPARs). PPARs arrange with heterodimers 9-cis retinoic acid receptor RXRa, which fix to distinguishing DNA arrangements designated as peroxisome proliferator response elements

PPREs, the isoforms of receptor PPAR α,β/δ,γ are recognized many agonist and antagonist are been highlighted in many review article.[6] Recently PPAR-δ activation by GW610742 renovates albuminuria by thwarting diabetes-induced nephrin loss and restoring podocyte integrity, implying that GW610742 may be a potential therapeutic agent for diabetic nephropathy.[6]

Thiazolidinediones (TZDs) are agent which reduce blood glucose level by reducing insulin resistance, through stimulation of a certain type of nuclear receptor, called peroxisome proliferator-activated receptor- γ (PPARγ).[7] Thiazolidinedione's, pioglitazone reduces urinary albumin secretion and prevent podocyte injury, suppress the loss of anionic site in glomerular basement membrane.[8] NIP-222 is a novel Peroxisome proliferator-activated receptor (PPAR) gamma agonist compound which causes regressions urinary albumin excretion (UAE) in diabetic mice NIP-222 has PPAR gamma autonomous effects on UAE in diabetic mice and propose that this agent may have prospective to minimize the progress and advancement of diabetic nephropathy.[9] Pioglitazone has filibustering effects on impaired glucose tolerance and urinary albumin excretion in diabetes. Glomerular hyper filtration may be due to endothelial constitutive nitric oxide synthase is suggested as one of the mechanisms for hyperfilteration. It emerges that the pioglitazone reduce of UAE may be related to enhancement of glomerular enlargement, including hyperfiltration, since the tissue levels of endothelial constitutive nitric oxide synthase protein were reduced by Pioglitazone in the glomerular vessels .[10] Pioglitazone has an antiproliferative effect and reduces extracellular matrix fabrication by means of reducing tissue inhibitor of metalloproteinase 1 and 2 activity, autonomously of TGF-beta.[11] Amelioration of diabetes and insulin resistance may occur adiponectin dependently in the liver and adiponectin independently in skeletal muscle with use of pioglitazone.[12] Management with PPAR gamma agonist has shielding effects on succession of glomerulosclerosis.[13] TZDs on G1-phase cell cycle arrest, the characteristic in diabetic nephropathy, pioglitazone considerably reticent glomerular hypertrophy and mesangial matrix enlargement and abridged urinary albumin emission pioglitazone upturned high glucose-induced G1-phase cell cycle arrest, i.e., an augment in G0/G1 phase and decline in S and G2 phases. Hyperglycaemia induced phosphorylation of p44 and 42 mitogen-activated protein kinase and abridged Bcl-2 and p27 (Kip1) protein levels are controlled as well as regulated by pioglitazone. Furthermore pioglitazone restored, repaired and controlled diabetic nephropathy by regulating cell cycle-dependent mechanisms apart from lowering blood glucose level.[14] Reduces synthesis of TGF-BETA and collagen IV. [15] Tesaglitazar not only reformed and overcome insulin resistance, glycaemic controller and regulator and inconsistent and abnormal lipid profile but also significantly decreased albuminuria and renal glomerular fibrosis in db/db mice investigational study model. These data assemblage help the utility of dual PPAR alpha or gamma agonists in management type 2 diabetes and diabetic nephropathy.[16] In DN, highly reactive biological end products which interacts with various biomolecules inside the cell and are called as AGEs which play a prominent role via generation of extracellular matrix (ECM) accumulation as result of hyperglycaemia. A major inhibitor of plasminogen activator- plasminogen activator inhibitor-1 (PAI-1), that plays an imperative role in degrading extracellular matrix, considerably augment in renal fibrotic diseases PPAR-gamma agonist can allay these AGEs effects via suppressing PAI-1 expression. Rosiglitazone (PPAR-gamma) agonist augmented recovery against highly biological reactive end products AGE-induced kidney ECM accumulation, proteinuria, and PAI-1 upregulation. Renal shielding effect of rosiglitazone from highly reactive AGEs conceivable protective mechanism could be associated with the overpowering of PAI-1 expression through PPAR-dependent and independent mechanisms.[16] Pioglitazone down-regulated multiple pro inflammatory and inflammatory and pro-fibrotic genes which contribute to kidney damage such as NF-kappa B , CCL2, TGFbeta1, PAI-1 and VEGF, pioglitazone not only changed but also recuperate and overwhelmed insulin resistance, glycaemic control and regulated and abnormal and inconsistent lipid profile, through an anti-inflammatory mechanism in type 2 diabetic repair renal polemic.[17] Pioglitazone restrained endothelial tumour necrosis factor (TNF) α induced VCAM-1 messenger RNA appearance and promoter activity, pioglitazone control inflammatory target genes in hepatic tissue (I kappa B alpha) and endothelial cells of blood vessels (VCAM-1) settings in a PPAR alpha-dependent manner.[18] PPAR-gamma agonist conspicuously curtailed TGF-beta signalling pathway and diminished renal interstitial fibrosis and inflammation in the animal model.[19] The amalgamation of immunosuppressant calcineurin inhibitor sirolimus and rosiglitazone is having shielding effects on kidney in diabetic nephropathy.[20] Rosiglitazone prevent albuminuria and nephrin down regulation in investigational diabetes model along with glycaemic control and blood pressure control. This outcome is probable ensues via rectification of diabetes-induced inflammatory processes .[21] Traditional medicine Honokiol, a Chinese remedy acquired from magnolia bark has displayed partial non-adipogenic PPAR-γ agonist in vitro which prohibited hyperglycaemia and weight gain in vivo. It has a prospective to develop as anti-diabetic nephropathy agent.[22] Improve the expression of klotho.[23] PPAR-δ activation by GW610742 improved albuminuria by checking diabetes-induced nephrin loss and renovating podocyte integrity, entailing that GW610742 may be impending therapeutic instrument for diabetic nephropathy. Shielding against drugs-induced nephrotoxicity the mechanism is PPAR-γ agonists preserve intracellular antioxidant.[24] Thwarts podocytopathy the fundamental mechanism mechanisms reverting of G1-phase cell circle, obstruction of stretch-induced AT 1 receptor upregulation, anti-apoptosis effect

prevents mitochondrial dysfunction, podocyte protective.[25-28] PPAR-γ plays role in renal metabolism and systemic homeostasis. [27]

SUMMARY OF ACTION OF TZDS[1,5,29-39]

Decline in NEFA upsurge in HDL cholesterol, upsurge in LDL cholesterol particle proportions, decline (with pioglitazone) or upsurge (with rosiglitazone) in triglycerides, reduction in blood pressure improvement in endothelial function, reduction in pulse wave velocity, reduction in vascular intima-media thickness, reduction in visceral fat, upsurge in subcutaneous fat, reduction in hepatic fat content, reduction in PAI-1 levels and activity, reduction of platelet aggregation, reduction in C-reactive protein, reduction in TNF-α, reduction in (MCP-1) monocyte chemo attract protein-1, decline in matrix metalloproteinase-9, thiazolidinedione's probably contribute to decrease UAE and reduction of renal injury, blood glucose decrease, reduction in plasma insulin levels, blood pressure depressing, restrain the glomerular and tubular cell proliferation, reduction in extracellular matrix production, TGF-β and other growth factors, decrease of pro-inflammatory cytokines and inflammatory processes, down-regulation of RAAS, enhancement in renal endothelial function, decline of oxidant stress at the kidney level, reduction of renal endothelin-1 levels and actions, decline of blood plasma PAI-1 levels and glomerular expression of PAI-1, attenuation of the decrease in matrix metallo-proteinases.

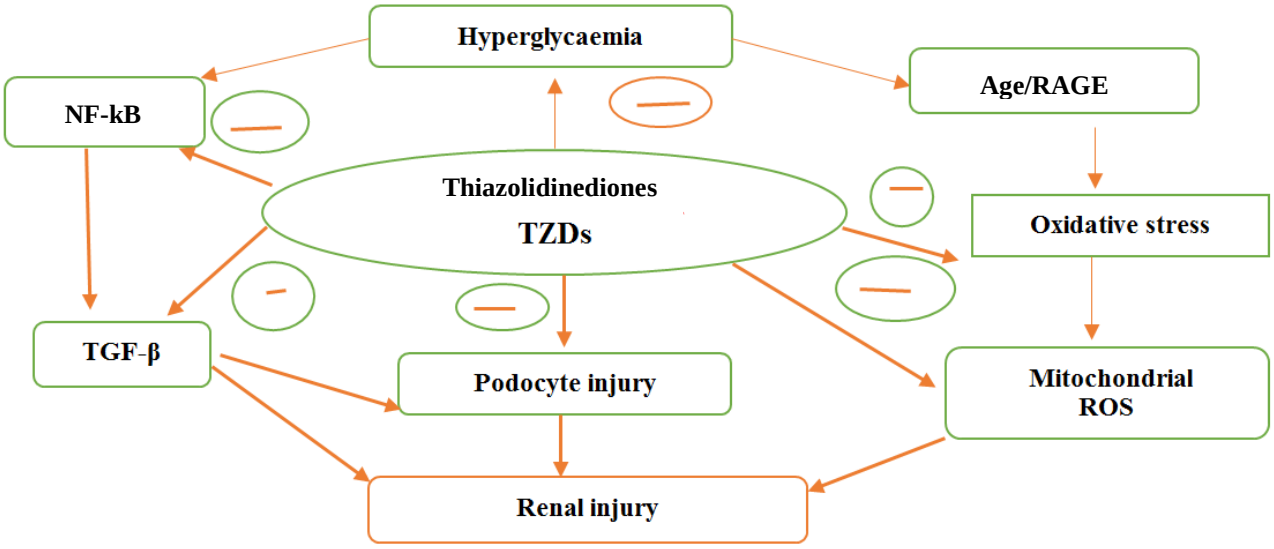

Figure 1: Cellular action of TDZs.

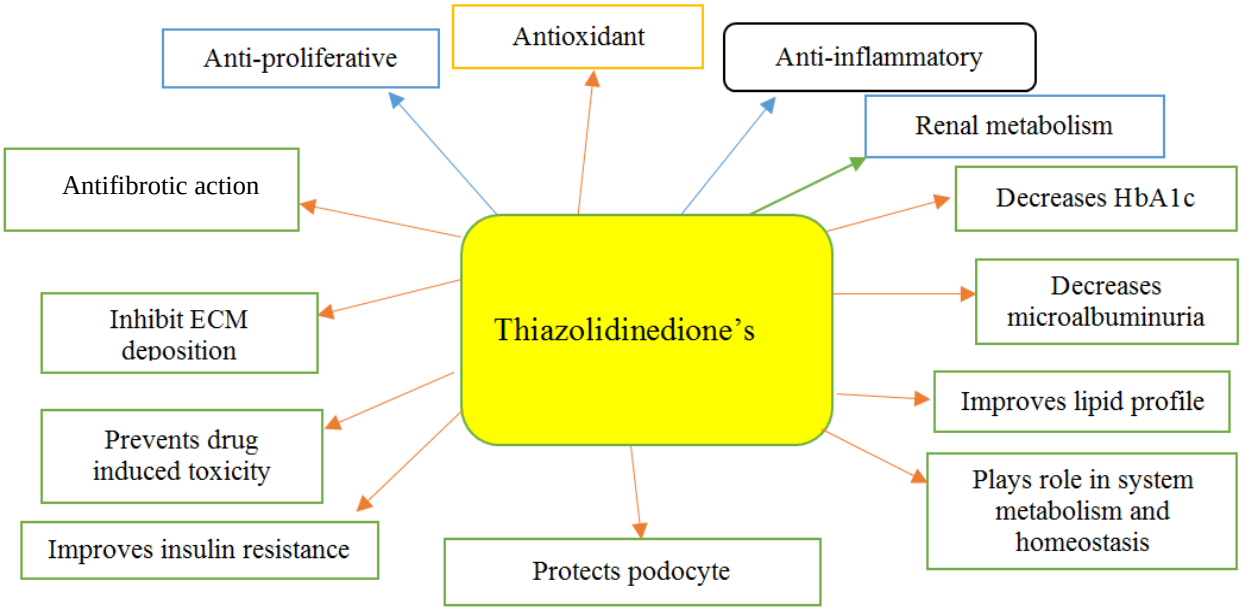

Figure 2: Pharmacological action of TZDs.

DUAL ACTIVATORS

Dual activation of PPAR-α and PPAR-γ i.e., PPARα is disseminated in numerous tissues together with the kidney suggesting its role in diabetic nephropathy. Animal study by combined low quantity of PPARα agonist fenofibrate and low amount of PPARγ agonist rosiglitazone gave better result than in diabetic kidney than individual drug. Moreover, the dual PPAR or agonist may have future prospective for development.[25]

SELECTIVE PPAR

Modulators (SPPARγMs) balaglitazone is the noticeable candidate currently under clinical experimented in Europe. Statistics from the clinical records displayed a strong anti-diabetic effect of balaglitazone. Further statistics from animals study point out that no substantial fluid withholding, no weight gain, no cardiac hypertrophy.[25]

Side effects

Factual side effects including fluid preservation, cardiovascular impediments, hepatotoxicity, cardio-myocytes hypertrophy, congestive heart failure possibly occur due to the fluid retention. Troglitazone hepatotoxicity, rosiglitazone considerably linked with the amplified threat of cardiovascular complications including heart failure and myocardial infarction pioglitazone, it has been supposed to have altered safety profile. But, it still preserves the effects of weight gain, bone loss (osteoporosis), oedema, bladder cancer and fluid retention which lead congestive heart failure.[5,25]

Take home message

PPAR-γ is versatile target having numerous benefits and mainly preventing fibrosis in diabetic experimental model and some clinical case report yet, the benefits are not up to mark, since renal failure itself causes volume expansion and the TZDs also retain salt and water and lead to congestive heart failure which restrains its clinical application. Dual activators and balaglitazone selective PPAR modulator are having potential for treatment of diabetic nephropathy. Further detail investigation on such drug is needed to explore.

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