Review Article

Peroxisome proliferator-activated receptor-alpha agonists in the management of the diabetic acute kidney injury: Is the verdict out?

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ABSTRACT

The growing evidences of diabetic acute kidney injury (AKI) suggested that diabetes is one of the detrimental causes. AKI is associated with glomerular hypertrophy, glomerulosclerosis, tubulointerstitial fibrosis, and mesangial cell expansion followed by albuminuria and reduction in glomerular filtration rate. Indeed, no promising therapeutic options are available in the present clinical scenario to manage efficiently the AKI. However, angiotensin-converting enzyme inhibitors and angiotensin-II-AT (1) receptor blockers are currently employed to improve the structural and functional status of the AKI. These interventions, however, are not optimal in improving overall outcomes of AKI. Hence, there is a continuing need for developing promising therapeutic interventions to manage this insidious condition adequately. Recent bench and clinical studies strongly suggest the potentials of peroxisome proliferator-activated receptor alpha (PPAR-α) agonists in the management of AKI by keeping the view that renal lipid accumulation-induced lipotoxicity is one of the risk factors for nephropathy during chronic diabetes mellitus. As inflammation, oxidative stress and dyslipidemia are common consequences of renal dysfunction, PPAR-α agonists could serve as promising therapeutic agents for controlling the progression of AKI. In fact, fenofibrate, a hypolipidemic agent acts as a PPAR-α agonist, reduced renal lipotoxicity, inflammation, fibrosis, and oxidative stress, and subsequently prevented the symptoms of diabetic nephropathy. However, fenofibrate has been shown to cause renal dysfunction in established renal disorders. The present review addressed the rationale of employing PPAR-α agonists in the management of AKI.

Keywords: Acute kidney injury failure, diabetes, nephopathy

Introduction

ARF is a life-threatening condition whose mortality remained high before the introduction of hemodialysis. It is an extremely morbid and costly condition with a significant proportion of patients progressing to end-stage renal disease (ESRD) need dialysis. It is also difficult for a nephrologist to manage ARF patients since the pathophysiology is not clearly understood and the limited therapeutic options. Dialysis remains the only FDA-approved treatment for acute renal failure, but dialysis may also cause renal injury that prolongs renal failure.[1]

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Acute kidney injury (AKI) is common (8–16% of hospital admissions), serious (four-fold increased hospital mortality), and many aspects of its natural history remain uncertain. In the United Kingdom, >1% of health service expenditure is attributed to AKI.

In diabetes, hyperglycemia, vascular endothelial dysfunction (VED), and hyperlipidemia are considered as possible reasons behind the pathogenesis and progression of diabetic nephropathy. The diabetes-mediated downregulation of VED is well documented. Further, diabetes medicated oxidative stress, VED and hyperlipidemia are played a central role in the pathogenesis of nephropathy.[2]

It is interesting that recent studies demonstrated numerous pleiotropic effects of peroxisome proliferator-activated receptor-alpha (PPAR-α) agonist such as fenofibrate and gemfibrozil. Gemfibrozil is well known to produce antihyperlipidemic action by activation of PPAR-α. In addition to this, upregulation of PPAR-α had an important role in

affording the protection against experimental acute kidney failure. Importantly, research exhibiting the most pronounced benefits of gemfibrozil in preventing vascular events by direct activation and protection of guanylyl cyclase (sGC) the key mediator of nitric oxide (NO) synthesis. The gemfibrozil mediated activation of guanylyl cyclase may be a rational concept to attenuate the oxidative stress and hyperlipidemia. Further, fenofibrate is well documented to attenuate diabetes-induced endothelial function by upregulating endothelial NO synthase (eNOS) and by decreasing oxidative stress and hyperlipidemia.[3,4] Further, the nephroprotective role of fenofibrate is reported in diabetes by ameliorating oxidative stress and hyperlipidemia. Furthermore, fenofibrate has been shown to reduce glomerular hypertrophy, mesangial matrix expansion and suppress the expression of plasminogen activator inhibitor-1 and transforming growth factor-b (TGF-b).[5] Therefore, the renovascular protective role of PPAR-α agonist may be a rational therapeutic strategy to ameliorate AKI.

Diabetes-induced Kidney Injury

Diabetes mellitus is known to trigger retinopathy, neuropathy, and nephropathy. The cellular elements of the kidney, that is, glomerular endothelial, mesangial cells, podocytes, and tubular epithelia, are targets for hyperglycemic injury. Glomerulosclerosis, thickening of the glomerular basement membrane, glomerular hypertrophy, mesangial cell expansion, podocyte loss, renal-cell hypertrophy, and tubulointerstitial fibrosis are among the major pathological changes that occur during the course of diabetic nephropathy, which ultimately results in progressive albuminuria, reduction in glomerular filtration rate (GFR), and elevation of arterial blood pressure and fluid retention.

Diabetic AKI (Nephropathy)

Diabetic nephropathy DN affects almost 40% of the diabetic individuals and is the major cause behind ESRD or kidney failure. DN affects the kidney's ability to remove waste products and extra fluid from the body. Diabetic nephropathy is clinically defined by the presence of proteinuria >0.5 g/24 h in diabetic patients which are preceded by lower degrees of proteinuria, or "microalbuminuria." Microalbuminuria is defined as urinary albumin excretion of 30–299 mg/24 h. Diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy if not properly treated with intervention. This type of progression can be observed in both Type-1 and Type-2 diabetic individuals.[6] It can be prevented by the maintenance of a healthy lifestyle and blood pressure within limits. Early treatment can prevent or slow disease progression and reduce the chance of complications. At the stage of ESRD, treatment options are dialysis or a kidney transplant.

Clinically, the patient shows hyperfiltration, represented by high values of GFR, and occasional occurrence of microalbuminuria at the initial stage of the disease. The duration of these abnormal data is approximately 5 years. Later, during a course of approximately 20 years, the patient shows a persistent decline of the GFR and continuous presence of microalbuminuria that comes before mild and subsequently moderate proteinuria. In the final step of the disease, severe proteinuria develops with or without nephrotic syndrome and chronic renal insufficiency that progress to ESRD.

In patients of DN following pathological remarks can be observed in the kidney such as increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation, glomerulosclerosis, thickening of the glomerular basement membrane, glomerular hypertrophy, mesangial cell expansion, podocyte loss, renal-cell hypertrophy, and tubulointerstitial fibrosis. All these pathological alterations ultimately result in functional consequences, including progressive albuminuria, reduction in GFR, elevation of arterial blood pressure, and fluid retention.[2,7-9]

Diabetic nephropathy can be screened using either a 24-h urine collection or a spot urine measurement of microalbumin among which spot measurements are more convenient for patients than 24-h urine collections. Measurement of the microalbumin-to-creatinine ratio may also help to account for concentration or dilution of urine. It is also important to exclude other conditions which also cause an increase in the excretion of protein in urine such as urinary tract infections, exercise, and hematuria.[10] All the kidney cellular elements, that is, glomerular endothelial, mesangial cells, podocytes, and tubular epithelia, are targets of hyperglycemic injury.

Increased Reactive Oxygen Species (ROS)

Under normal physiological conditions, approximately 0.1–5% of oxygen that enters the electron transport chain is reduced to superoxide; a ROS and the rest are used in metabolic processes and during this state, there is a balance in the generation of oxygen free radicals and antioxidant defense systems used by organisms to deactivate and protect themselves against free radical toxicity.

Antioxidant defense system includes ROS degrading molecules (ROS scavengers), such as uric acid, ascorbic acid, and sulfhydryl-containing molecules (e.g., glutathione), and antioxidant enzymes, such as catalase, glutathione peroxidase, and superoxide dismutases.

Oxidative stress describes a condition in which antioxidant defense is insufficient to keep the level of ROS below a toxic threshold. This may be due to either the excessive generation of ROS or loss of antioxidant defense or both. In diabetes-induced nephropathy endogenous antioxidant enzymes or phase, 2 antioxidant enzymes are mostly affected and causes oxidative damage produced by overproduction of ROS [Figure 1].]

Altered NO Availability and VED

Vascular endothelium is an interior lining of blood vessels and lies between circulating blood and the vascular smooth muscle cells. Endothelium regulates vascular tone and maintains the free flow of blood in vessels. VED has been characterized by reduced activation of eNOS, reduced generation and bioavailability of NO and increased production of ROS.

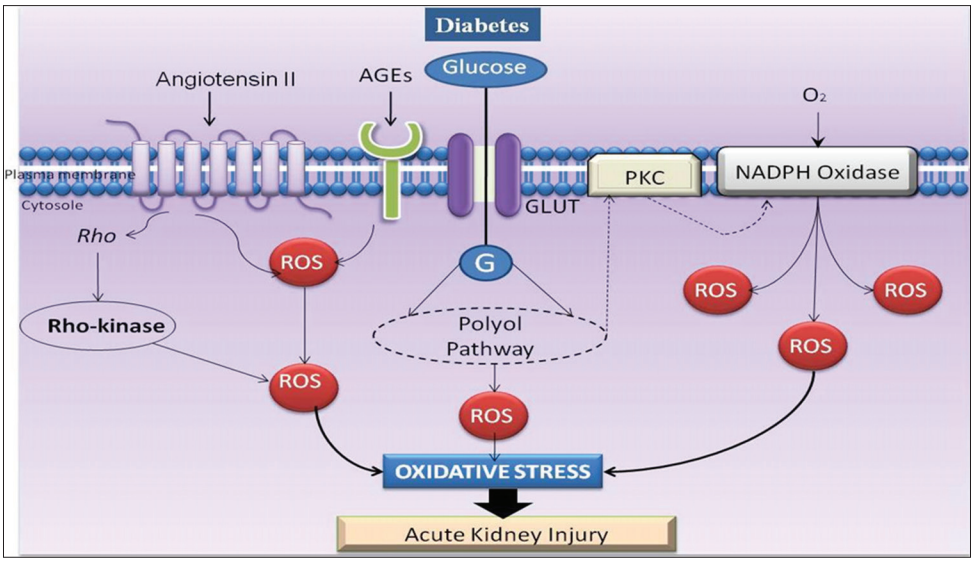

Figure 1: Mechanisam behind diabetes-induced acute kidney ijnury

VED has been associated with the pathogenesis of diabetes mellitus and nephropathy; the basic and clinical studies have demonstrated the strong correlation between diabetes and VED.[11,12] It has been demonstrated that hyperglycemia scavenges NO and induces VED, which ultimately results in nephropathy. NO also induces vasodilation and numerous studies have suggested that hyperglycemia-induced hemodynamic pathways play a detrimental role in the induction and progression of diabetic nephropathy and are recognized to be major mediators of kidney disease.

Abnormalities of NO production alter renal structure and function in diabetes. The complex metabolic environment in diabetes stimulates several pathophysiologic mechanisms that simultaneously increase and decrease NO production. The early phase of diabetic nephropathy is associated with increased intrarenal NO production mediated primarily by constitutively released NO through eNOS and neuronal NOS. The enhanced NO production may contribute to hyperfiltration and microalbuminuria that characterizes early diabetic nephropathy. Advanced diabetic nephropathy leading to severe proteinuria, declining renal function, and hypertension is associated with a state of progressive NO deficiency. Several factors including hyperglycemia, advanced glycosylation end products, increased oxidant stress, as well as activation of protein kinase C and TGF-β contribute to decreased NO production and/or availability. Changes in NO availability are mediated through multiple mechanisms such as glucose quenching, and inhibition, and/or posttranslational modification of NOS activity of both endothelial and inducible isoforms. There are studies which established that NO donor such as 2,2'-(hydroxynitrosohydrazino) bis-ethanamine can ameliorate pathological characteristics in an animal model of diabetic nephropthy.[13]

Altered lipid metabolism

Dyslipidemia is a condition commonly observed in diabetic individuals, associated with hypertriglyceridemia, elevated low-density lipoprotein levels, and decreased high-density lipoprotein levels.[14,15] The association between hyperglycemia and lipid accumulation is a hallmark of diabetic nephropathy. Insulin resistance in diabetes is the initial step in the formation of dyslipidemia. Furthermore, dyslipidemia has been suggested as an independent risk factor for the development and progression of diabetic nephropathy.[16]This indicates that insulin resistance/hyperinsulinemia is a primary cause of diabetic dyslipidemia. Thus, patients with diabetic nephropathy often have multiple lipoprotein abnormalities.[17] However, two key mechanisms explain the association between diabetes mellitus and hyperlipidemia. First, insulin deficiency down regulates the lipoprotein lipase (LPL), an enzyme involved in the hydrolysis and clearance of triglycerides from the circulation.[18] Second, insulin has an inhibitory action on 3-hydroxy-3-methyl-glutaryl-Co-A (HMG-COA) reductase, a key rate-limiting enzyme involved in the synthesis of cholesterol.[19]

Jointly, it is possible that hypoinsulinemia during long-term diabetes downregulates LPL and activates the HMG-COA reductase pathway and might play a role in excessive lipid accumulation during the early stages of diabetic nephropathy. The chronic diabetes mellitus may mediate renal injury by increasing the renal expression of SREBP-1, which is responsible for increasing the synthesis of triglycerides and cholesterol in the kidney.

Altered lipid profile during the diabetic state has been noted to be associated with the increased expression of TGF-β1, connective tissue growth factor, fibronectin, collagen IV, mitogen-activated protein kinases, and nuclear factor-kappa B which ultimately accounts for glomerulosclerosis and tubulointerstitial fibrosis. Treatment with lipid-lowering agents has shown to reduce glomerular lesion in an animal model of diabetic nephropathy.[20]

Role of PPAR-Alpha

Fenofibrate (1-methylethyl2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoate) and gemfibrozil (5-(2,5-dimethylphenoxy)-2,2-dimethyl-pentanoic acid) are a well-known activator of PPAR-αActivation of PPAR-α by its ligands promotes lipid

metabolism. In addition, PPAR-α is expressed in vascular endothelial cells, smooth muscle cells, macrophages, and T lymphocytes. PPAR-α agonists are shown to ameliorate VED by reducing oxidative stress and inflammation.[21] Further, fenofibrate has been noted to improve the function of endothelium by reducing the serum level of asymmetric dimethylarginine an endogenous inhibitor of NO synthetase, decreases the oxidative stress and increase the NO bioavailability. Experimental and clinical studies have shown the cardioprotective effect of fibrate class of PPAR-α agonists besides their hypolipidemic action.[22] PPAR-α agonists have anti-atherosclerotic activity, which is attributed to their inhibitory activity on various transcription factors.[23] A recent study showed the ameliorative effect of fenofibrate against cardiac hypertrophy and gemfibrozil mediated renopritection.[24,25] In addition, PPAR-α ligands have shown beneficial effects in reducing myocardial infarction by attenuating oxidative stress, apoptosis, and inflammation.[26,27]

The current research interest is to treat diabetic nephropathy by use of a fibrates class of interventions, such as fenofibrate, and gemfibrozil, and well-known hypolipidemic agents.[3,28] Recent *in vitro* study reported that gemfibrozil direct activation and protection of sGC function results in activation of secondary messenger cGMP in response to NO stimulation.[3]

Recently, in our laboratory, we have shown that treatment with fenofibrate and concurrent administration of benfotiamine, a transketolase activator, prevented the development of diabetic nephropathy. This renoprotective effect of fenofibrate was associated with its actions on reducing the circulating lipids and oxidative stress.[2] Furthermore, fenofibrate was shown to ameliorate nicotine-induced endothelial dysfunction by reducing hyperlipidemia and oxidative stress in rats.[29] Thus, the available evidence says that the use of fenofibrate attenuates diabetes and nicotine-mediated hyperlipidemia and oxidative stress and ameliorates endothelial dysfunction and nephropathy. Therefore, the use of PPAR-α agonists fenofibrate and gemfibrozil is the most logical pharmacological intervention to treat the smoking mediated progression of diabetic nephropathy, like killing two birds with one stone. From the above discussion, it may be concluded that fibrate really preserves kidney function in diabetes. Taken together, these studies suggest that these drugs may provide supportive therapeutic advancement for treating diabetic smokers with nephropathy.

Conclusion

PAR-α agonists could serve as promising therapeutic agents for controlling the progression of AKI. The fenofibrate and gemfibrozil both have antihyperlipidemic activity along with a reduction in the oxidative stress and hyperlipidemic activity and can be considered as a novel therapeutic target in the treatment of AKI.

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