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► **To cite this version:**

Moshe Levi. Nuclear receptors in renal disease. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, 2011, 10.1016/j.bbadis.2011.04.003 . hal-00706531

**HAL Id: hal-00706531**

**<https://hal.science/hal-00706531>**

Submitted on 11 Jun 2012

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## Accepted Manuscript

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PII: S0925-4439(11)00077-9  
DOI: doi: [10.1016/j.bbadis.2011.04.003](https://doi.org/10.1016/j.bbadis.2011.04.003)  
Reference: BBADIS 63278

To appear in: *BBA - Molecular Basis of Disease*

Received date: 13 January 2011  
Revised date: 21 March 2011  
Accepted date: 6 April 2011



Please cite this article as: Moshe Levi, Nuclear receptors in renal disease, *BBA - Molecular Basis of Disease* (2011), doi: [10.1016/j.bbadis.2011.04.003](https://doi.org/10.1016/j.bbadis.2011.04.003)

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# **NUCLEAR RECEPTORS IN RENAL DISEASE**

**Moshe Levi, MD**

**Department of Medicine, Division of Nephrology and  
Hypertension, University of Colorado Denver**

**12700 East 19th Avenue  
Research 2, Room 7002, Box C281  
Aurora, Colorado 80045  
Phone: 303-724-4825  
Fax: 303-724-4868  
E-mail: Moshe.Levi@ucdenver.edu**

**BBA – Molecular Basis of Disease**

**Revised 3/14/11**

**Abstract**

Diabetes is the leading cause of end-stage renal disease in developed countries. In spite of excellent glucose and blood pressure control, including administration of angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers, diabetic nephropathy still develops and progresses. The development of additional protective therapeutic interventions is, therefore, a major priority. Nuclear hormone receptors regulate carbohydrate metabolism, lipid metabolism, the immune response, and inflammation. These receptors also modulate the development of fibrosis. As a result of their diverse biological effects, nuclear hormone receptors have become major pharmaceutical targets for the treatment of metabolic diseases. The increasing prevalence of diabetic nephropathy has led intense investigation into the role that nuclear hormone receptors may have in slowing or preventing the progression of renal disease. This role of nuclear hormone receptors would be associated with improvements in metabolism, the immune response, and inflammation. Several nuclear receptor activating ligands (agonists) have been shown to have a renal protective effect in the context of diabetic nephropathy. This review will discuss the evidence regarding the beneficial effects of the activation of several nuclear, especially the vitamin D receptor (VDR), farnesoid X receptor (FXR), and peroxisome-proliferator-associated receptors (PPARs) in preventing the progression of diabetic nephropathy and describes how the discovery and development of compounds that modulate the activity of nuclear hormone receptors may provide potential additional therapeutic approaches in the management of diabetic nephropathy.

## **Introduction**

Diabetes mellitus is the most common cause of end-stage renal disease in the developed world requiring dialysis or renal transplantation for the maintenance of life. The pathogenesis of diabetic nephropathy is multifactorial. Hypertension, abnormal carbohydrate metabolism, abnormal lipid metabolism, accumulation of lipids, upregulation of profibrotic growth factors (including, renin, angiotensin II, transforming growth factor  $\beta$  [TGF- $\beta$ ] and vascular endothelial growth factor [VEGF]), upregulation of proinflammatory cytokines (including, nuclear factor kappa B [NF- $\kappa$ B], CCL2, also known as MCP1, tumor necrosis factor [TNF] and interleukin 1 $\beta$  [IL-1 $\beta$ ]), increased oxidative stress, and increased production of advanced glycation end products all have an important role in the pathogenesis and progression of diabetic nephropathy[1-4].

In spite of all the beneficial interventions implemented in patients with diabetes, including tight glucose control, tight blood pressure control, and angiotensin II receptor antagonism, renal injury progresses in most of these patients. Additional treatment modalities that modulate the pathogenetic pathways involved in diabetic nephropathy are urgently needed to slow the progression of renal failure in patients with diabetes.

Studies in humans with type 1 or type 2 diabetes mellitus and in animal models of these diseases have reported an accumulation of lipids (triglycerides and cholesterol) in the kidney—even in the absence of abnormalities in serum lipid levels—which is associated with the development of glomerulosclerosis, tubulointerstitial fibrosis, and the progression of diabetic renal disease[5-13]. The accumulation of triglycerides and cholesterol in the kidney is mediated by increased expression and activity of the transcriptional factors the sterol regulatory element binding proteins 1 and 2 [SREBP-1 and SREBP-2] which are master regulators of fatty acid and cholesterol synthesis. We have therefore become interested in nuclear receptors that are potential negative regulators of SREBPs and also inflammation, oxidative stress, and fibrosis and therefore may slow down the progression of diabetic kidney disease.

This review discusses nuclear hormone receptors thought to have a role in the pathogenesis of kidney disease, especially diabetic nephropathy, including the vitamin D receptor (VDR), farnesoid X receptor (FXR), and peroxisome-proliferator-associated receptors (PPARs).

## **Vitamin D Receptor**

Vitamin D<sub>3</sub> is acquired either from dietary sources or is generated via solar ultraviolet irradiation of 7-dehydrocholesterol in the skin. Vitamin D<sub>3</sub> is then processed into the active hormone, 1,25 dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>), via two consecutive hydroxylation reactions[14-15]. The first such reaction takes place in the liver and is catalyzed by 25-hydroxylase and the second is catalyzed by 1 $\alpha$ -hydroxylase, which is expressed predominantly in the kidney. Extrarenal 1,25(OH)<sub>2</sub>D<sub>3</sub> can also be produced locally in a number of cell types that express VDR, notably cells of the skin, immune system, colon, pancreas, and vasculature. Locally produced 1,25(OH)<sub>2</sub>D<sub>3</sub> does not contribute significantly to circulating 1,25(OH)<sub>2</sub>D<sub>3</sub> levels, but it retains the capacity to be active in the cells and tissues where they are produced.

The activity of 1,25(OH)<sub>2</sub>D<sub>3</sub> is mediated by VDR. 1,25(OH)<sub>2</sub>D<sub>3</sub>-VDR has multiple physiological and pathological roles that extend beyond the regulation of mineral metabolism, including the

regulation of renal and cardiovascular functions. Naturally occurring, low-affinity VDR ligands that have been identified over the past 2 years (for example, lithocholic acid, curcumin, and polyunsaturated fatty acids) may trigger  $1,25(\text{OH})_2\text{D}_3$ -independent activation of VDR in specific tissues [16].  $1,25(\text{OH})_2\text{D}_3$  can also induce rapid nongenomic effects on target cells in the vitamin D endocrine system regulated by vitamin D.

Although VDR may not be involved in this pathway as rapid actions of  $1,25(\text{OH})_2\text{D}_3$  can be elicited in the absence of VDR, the nongenomic pathway regulated by  $1,25(\text{OH})_2\text{D}_3$  can interact with genomic pathway to modulate VDR-dependent gene expression [17].  $1,25(\text{OH})_2\text{D}_3$  rapid activation of cytosolic kinases via nongenomic pathway has been shown to lead to the phosphorylation of critical co-activators of VDR, resulting in modulation of VDR-dependent gene transcription [17]. VDR may also exert direct effects on the nucleus and form complexes with the p65 subunit of NF $\kappa$ B and thus cause repression of p65-mediated gene transcription. This expression inhibition results in an anti-inflammatory effect [18].

Immunohistochemical studies indicate that VDR is expressed in proximal and distal tubular epithelial cells, glomerular parietal epithelial cells, and collecting duct cells; VDR is also expressed by cultured podocytes and mesangial cells [19-21].

A link between the development of type 1 diabetes mellitus and vitamin D deficiency has been well described, and a 2008 meta-analysis of five observational studies suggested that children who receive vitamin D supplementation have a reduced risk of developing type 1 diabetes mellitus [22]. Over the past 5 years, a number of large observational studies have also suggested an association between the onset of type 2 diabetes mellitus and vitamin D deficiency [23]. Vitamin D deficiency is also very common in patients with chronic kidney disease (CKD), perhaps in part because diabetes is the most common cause of CKD [24-25].

VDR agonists have been shown to be protective in mouse models of diabetes mellitus. The studies in mice with type 1 diabetes mellitus and type 2 diabetes mellitus have shown that the renal protective effects of VDR agonists are mediated by inhibition or antagonism of the renin angiotensin system [26-31] and NF- $\kappa$ B [18, 20, 32] which are major mediators of increased intraglomerular pressure, podocyte damage, oxidative stress, inflammation, and fibrosis. In addition, VDR agonists activate hepatocytes growth factor and prevent renal interstitial myofibroblast activation [33-34]. In contrast, VDR knockout mice have been shown to be more susceptible to streptozotocin induced diabetic kidney disease in part via activation of the renin angiotensin system [35]. In this regard, VDR agonists in combination therapy with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II type 1 receptor blocker (ARB) have synergistic effects in development of kidney disease in rats with subtotal nephrectomy [36] and in mice with diabetes [37-39].

Recently we investigated if treatment of mice with diet induced obesity (DIO) and insulin resistance with the vitamin D receptor (VDR) agonist doxercalciferol ( $1\alpha$ -hydroxyvitamin D<sub>2</sub>) prevents renal disease. DIO and insulin resistance in mice is associated with proteinuria, renal mesangial expansion, accumulation of extracellular matrix proteins, and activation of oxidative stress, proinflammatory cytokines, profibrotic growth factors, and the sterol regulatory element binding proteins, SREBP-1 and SREBP-2 that mediate increases in fatty acid and cholesterol synthesis [12]. Kidney VDR expression was decreased in the DIO mice and treatment with doxercalciferol increased VDR expression in the kidney. Our results indicate that treatment of DIO mice with the VDR agonist decreases proteinuria, podocyte injury, mesangial expansion, and extracellular matrix protein accumulation. The VDR agonist also decreases macrophage infiltration, oxidative stress, proinflammatory cytokines and profibrotic growth factors. Furthermore the VDR agonist also prevents the activation of the renin angiotensin aldosterone system including the Angiotensin II type 1 Receptor (AT1R) and the Mineralocorticoid Receptor (MR). An additional novel finding of our study is that activation of VDR results in decreased accumulation of neutral lipids (triglycerides and cholesterol) and expression of adipophilin in the kidney by decreasing SREBP-1 and SREBP-2 expression and target enzymes that mediate fatty acid and cholesterol synthesis[40].

Treatment of DIO mice with doxercalciferol also increased the expression of the bile acid activated nuclear hormone receptor farnesoid X receptor (FXR) and bile acid activated G protein coupled receptor TGR5. Previous studies have indicated that bile acids activate VDR [41-42]. Recent studies also indicate that VDR agonists can increase portal bile acid concentration and trigger FXR like effects in the liver and the intestine in rats [43]. In further support of our findings VDR knockout mice have decreased FXR expression in the ileum, and treatment of mice with calcitriol increased FGF15 expression in the ileum which is a known FXR target [44]. Clearly our results warrant further investigation into how these two nuclear receptors cross-talk.

VDR agonists also play a protective role in several non-diabetic models of renal disease, including in mice and rats with Heyman Nephritis [45], anti-thy-1 model of mesangial proliferative glomerulonephritis [46-48], subtotal nephrectomy [49-51], puromycin aminoglycoside induced podocyte damage [52] and unilateral ureteral obstruction [53].

VDR agonists have also been shown to decrease proteinuria in human subjects with chronic kidney disease [54-56] and IgA nephropathy [57], and improve survival in patients with late stage ESRD [58]. A recent large scale randomized controlled study (VITAL) in patients with type 2 diabetes mellitus who were already been treated with ACE inhibitors or ARBs showed that treatment with paricalcitol resulted in a significant reduction in urinary albumin [59]. These studies therefore indicate that in addition to animal models of obesity, insulin resistance, and diabetes, VDR agonists are also highly beneficial in human subjects with diabetic or non-diabetic kidney disease.

## **Farnesoid X Receptor**

FXR is an adopted orphan nuclear receptor named after farnesol, an intermediate in the mevalonate biosynthetic pathway, which was found to weakly activate FXR at supraphysiological concentrations [60-61]. Subsequently endogenous bile acids were found to

bind to and activate FXR and FXR was found to have a critical role in the regulation of bile-acid metabolism [62-64]. The hydrophobic bile acid chenodeoxycholic acid and its conjugated forms are the most potent endogenous agonists of FXR, whereas the hydrophilic bile acids ursodeoxycholic acid and muricholic acid do not activate this receptor. Ligand-activated FXR can bind to and activate or repress the transcription of a large number of genes either as a FXR-retinoid X receptor (RXR) heterodimer or as a monomer [65].

FXR is highly expressed in the liver, intestine, adrenal gland, and with particularly high expression in the kidney [66]. Activation of FXR has an important role in maintaining glucose, lipid, and bile acid homeostasis in the enterohepatic system [67-68]. In addition, FXR activation prevents rat liver fibrosis induced with porcine serum or bile duct ligation [69] FXR activation also prevents atherosclerosis in LDL Receptor knockout mice and ApoE knockout mice [70-71] and vascular calcification on ApoE knockout mice with chronic kidney disease[72].

GW4064 which was the first synthetic high-affinity, nonsteroidal FXR agonist to be developed has been tested in rodent studies and in vitro cell cultures [67-68]. However, the poor bioavailability of GW4064 has limited its clinical development. The high-affinity, semi-synthetic, bile acid-derived FXR agonist, INT-747 (6 $\alpha$ -ethyl-chenodeoxycholic acid) was subsequently developed and has exhibited anticholestatic and antifibrotic properties in rodent models of liver disease [67]. A clinical trial is in progress to examine the physiological effect of FXR activation by INT-747 in humans with nonalcoholic fatty liver disease [67].

In mouse kidney, FXR has been detected in both isolated glomeruli and proximal tubules. The expression level in proximal tubule cells is much higher than in glomeruli [73]. In addition, FXR is expressed in both cultured mouse mesangial cells and podocytes [73].

FXR (Nr1h4) knockout mice with streptozotocin-induced type 1 diabetes leads develop increased renal injury compared with wild-type C57BL/6 mice with streptozotocin-induced type 1 diabetes[74]. These mice demonstrate increases in proteinuria, glomerulosclerosis, tubulointerstitial fibrosis, mesangial expansion, podocyte damage and glomerular basement membrane thickening. There is also increased macrophage infiltration, as well as increased expression of SREBP-1 and SREBP-2 that result in increased renal triglyceride and cholesterol content.

In contrast treatment of db/db mice with type 2 diabetes [73], in DBA/2J mice with diet-induced obesity and insulin resistance [75], and DBA/2J mice with streptozotocin-induced type 1 diabetes [74] with FXR agonists has marked renal protective effects. These experimental models of diabetic nephropathy showed improvements in proteinuria, glomerulosclerosis, tubulointerstitial fibrosis, and macrophage infiltration following treatment with FXR activating agonists. These renal protective effects are mediated by effects on lipid metabolism, oxidative stress, and on the production of proinflammatory cytokines and profibrotic growth factors [73, 75]. FXR agonists inhibit expression of SREBP-1 and carbohydrate response element binding protein (ChREBP) in the kidney resulting in decreased fatty acid synthesis and triglyceride accumulation [73-75].

FXR agonists also inhibit SREBP-2 resulting in decreased cholesterol synthesis and accumulation in the kidney. These studies suggest that FXR agonists can prevent the progression

of kidney disease in mouse models of type 1 diabetes mellitus, diet induced obesity and insulin resistance, and type 2 diabetes mellitus.

## **Peroxisome-Proliferator-Associated Receptors**

Three PPAR subtypes (PPAR $\alpha$ , PPAR $\gamma$  and PPAR $\delta$ ) have been cloned and characterized, each is encoded by its own gene and each has a unique tissue distribution [76].

### **Peroxisome-proliferator-associated receptor $\alpha$**

PPAR $\alpha$  is predominantly expressed in the proximal tubules and in the medullary thick ascending limb of Henle. Renal PPAR $\alpha$  has an important role in modulating energy utilization in the kidney through the regulation of renal fatty-acid  $\beta$ -oxidation. The importance of this role is made evident by the response of renal PPAR $\alpha$  to dietary lipids [77-78] and the protective effect of PPAR $\alpha$  against ischemia/reperfusion injury, in which the reduced renal fatty-acid oxidation results in the accumulation of fatty acid and cellular toxicity contributing to proximal tubule cell death [79-80]. PPAR $\alpha$  activation is also involved in the regulation of blood pressure through activation of the cytochrome P450 enzyme system in the proximal tubules [81]. Glomerular expression of PPAR $\alpha$  was reported to be very low [82]; however, induction of PPAR $\alpha$  expression has been observed in mouse mesangial cells after stimulation with lipopolysaccharide—a process which could contribute to the attenuation of lipopolysaccharide-induced inflammatory responses [83]. A study in PPAR $\alpha$  knockout mice demonstrated that PPAR $\alpha$  protects against glomerulonephritis through its anti-inflammatory effects, which suggests that PPAR $\alpha$  has an important role in protection against glomerular disease [84].

Accumulating evidence suggests that modulation of PPAR $\alpha$  activation could be beneficial in the management of diabetic nephropathy. PPAR $\alpha$  knockout mice with streptozotocin-induced type 1 diabetic mice have increased plasma free fatty acid and triglyceride levels and enhanced diabetic nephropathy, as evidenced by increased mesangial area expansion and albuminuria compared with wild-type diabetic mice. These effects are associated with an upregulation of profibrotic, proinflammatory, and proapoptotic pathways in glomeruli [85]. By contrast, treatment of db/db mice with type 2 diabetes with the PPAR $\alpha$  agonist fenofibrate reduces urinary albumin excretion, glomerular mesangial expansion, hyperglycemia, and insulin resistance [86]. A renal protective effect of PPAR $\alpha$  activation has also been documented in animal models with nephropathy induced by type 1 diabetes mellitus [87-89]. Administration of PPAR $\alpha$  agonists also has beneficial effects in humans with diabetic nephropathy. For example, administration of bezafibrate is renal protective in patients with diabetic nephropathy caused by type 2 diabetes [90]. This renal protective effect is associated with a reduction in urinary albumin excretion and in levels of circulating lipids [90]. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate administration was associated with a significant reduction in the rate at which albuminuria progresses in patients with type 2 diabetes [91].

PPAR $\alpha$  agonist may slow the progression of diabetic nephropathy by several diverse mechanisms. Activation of PPAR $\alpha$  may ameliorate diabetic nephropathy by exerting beneficial systemic effects, for example, by reducing circulating levels of glucose, insulin and lipids. PPAR $\alpha$  activation may also exert renal-specific effects that mediate renoprotection in diabetic

nephropathy. Stimulation of fatty-acid  $\beta$ -oxidation via activation of PPAR $\alpha$  provides a potential mechanism by which the lipid content of tissues could be reduced to prevent lipid accumulation and lipotoxicity. However, studies to investigate whether this mechanism takes place in the diabetic kidney have not yet been performed. Studies on macrophage and lipid-loaded mesangial cells suggest that PPAR $\alpha$  activation can directly regulate cholesterol homeostasis and foam-cell formation [92-93], processes which have important roles in the development of lipotoxic effects and inflammation in diabetic nephropathy. The anti-inflammatory and antinitrosative effects of PPAR $\alpha$  in animal models of diabetic nephropathy [85, 89] could relate to the ability of PPAR $\alpha$  to inhibit the activation of NF $\kappa$ B, an obligatory step in the synthesis of proinflammatory cytokines and inducible nitric oxide synthase, a major inducer of nitrosative stress. Whether PPAR $\alpha$  has a role in reducing oxidative stress induced by renal NADPH oxidase has not been examined. A direct effect of PPAR $\alpha$  in the kidney is supported by the fact that the PPAR $\alpha$  agonist fenofibrate blocked the adhesion of leukocytes to mesangial cells induced by high levels of glucose and suppressed the expression of type I collagen, type IV collagen and TGF- $\beta$  in mesangial cells treated with high levels of glucose [85-86]. Taken together this evidence suggests that, in addition to their lipid-lowering effects, PPAR $\alpha$  agonists also have therapeutic potential in preventing the progression of diabetic nephropathy.

### **Peroxisome-proliferator-associated receptor $\gamma$**

The role of PPAR $\gamma$  agonists (glitazones) in preventing the development and progression of diabetic nephropathy has been reported in numerous studies. The administration of a glitazone was found to be renal protective in the obese Zucker rat model of type 2 diabetes. In these animals, troglitazone decreased urine protein excretion and reduced blood glucose, blood pressure, plasma insulin, and plasma lipids [94]. Since then, a beneficial effect of glitazones on diabetic nephropathy has been consistently reported for in animal models of both type 1 and type 2 diabetes. In many of these studies, the reduction of albuminuria induced by glitazones was accompanied by a reduction of glomerular hyperfiltration and prevention of glomerulosclerosis and tubulointerstitial fibrosis [95].

Several clinical studies have examined the renal protective properties of glitazones in patients with type 2 diabetes. In most studies, glitazone treatment resulted in a significant reduction in albuminuria [95]. Glitazone treatment had a greater antiproteinuric effect than other oral hypoglycemic agents, such as metformin and glibenclamide, at doses that achieved of similar glycemic control [95-96]. In addition one retrospective case-controlled study [97] and one prospective study [98] have suggested that TZDs (glitazones) slow the progression of renal disease in patients with type 2 diabetes mellitus. Some adverse effects of long-term glitazone treatment have been observed, including hepatitis, weight gain and fluid retention[99], which has led to the withdrawal of troglitazone, and increasing warnings regarding rosiglitazone which has been associated with an increased risk of heart failure.

As the PPAR $\alpha$  agonist fenofibrate decreased food intake and the development of fat deposits induced by rosiglitazone in obese ob/ob mice [100], combination treatment with agonists of PPAR $\alpha$  and PPAR $\gamma$  or treatment with a dual agonist of both receptors may reduce adverse effects associated with PPAR $\gamma$  activators and induce a synergistic beneficial effect in preventing the development of diabetic nephropathy. Although direct comparative studies of the effectiveness

of combination agonism versus dual agonism of PPARs have not been performed, treatment with a PPAR $\alpha$ /PPAR $\gamma$  dual agonist protected db/db mice against glomerular and interstitial damage and improved insulin resistance, glycemic control and lipid profile [101].

The mechanisms by which PPAR $\gamma$  agonists modulate diabetic nephropathy have been reviewed elsewhere [96]. Normalization of hyperglycemia, hyperlipidemia and hypertension by glitazone treatment may be important in preventing the renal complications of diabetes. In addition, studies in animal models, in isolated glomeruli, and in renal cell cultures also indicate that glitazones have direct actions on renal cells. In mesangial cells and in proximal tubule cells, PPAR $\gamma$  agonists have antiproliferative, antifibrotic, and anti-inflammatory effects [96]. In animal models of type 2 diabetes, activation of PPAR $\gamma$  prevents renal endothelial cell dysfunction and podocyte injury, and inhibits activation of NF $\kappa$ B, the accumulation of reactive oxygen species, and infiltration of macrophages in the kidney [96, 102]. Studies in mesangial cells suggest that PPAR $\gamma$  may regulate renal lipid metabolism by activating the LXR $\alpha$ -ATP-binding cassette 1 pathway to facilitate cholesterol efflux, suggesting a possible mechanism for our more recent observations [103].

### **Peroxisome-proliferator-associated receptor $\delta$**

To date no studies have investigated the role of PPAR $\delta$  in diabetic nephropathy, and no clinical studies have investigated the use of PPAR $\delta$  agonists. In the Akita and the OVE26 mouse models of type 1 diabetes, renal expression of PPAR $\delta$  is greatly suppressed compared with wild-type mice [11]. When exposed to oxidized lipids, which are ubiquitously produced in the renal tubules of animal models of diabetic nephropathy, proximal tubular cells of obese, diabetic rats showed suppression of PPAR $\delta$  expression [104]. These data suggest a potentially important role for PPAR $\delta$  in diabetic nephropathy. In mouse models of ischemia-induced renal injury, administration of a synthetic PPAR $\delta$  agonist was associated with strong renal protection and a reduction in medullary necrosis, apoptosis, and inflammation [105]. The role of PPAR $\delta$  in ameliorating inflammation and regulating lipid metabolism in animal models of disease such as ischemia-induced injury suggests that PPAR $\delta$  agonists may also confer renal protection in diabetic nephropathy.

### **Estrogen receptors**

Both estrogen receptor  $\alpha$  and estrogen receptor  $\beta$  are found in the kidney, although estrogen receptor  $\alpha$  is the predominant isoform. Estrogen receptor  $\alpha$  and estrogen receptor  $\beta$  are expressed in glomeruli and in isolated mesangial cells [106-107]. Immunohistochemical studies have also identified the expression of estrogen receptors on podocytes [108]. Estrogen receptor  $\alpha$  is the dominant estrogen receptor in terms of its effects, and the kidney is an organ where the effects of estrogen receptor  $\alpha$  are particularly prominent [109]. The role of estrogen receptor  $\beta$  in the kidney is less clear than that of estrogen receptor  $\alpha$ , but it has been suggested to be a dominant repressor of estrogen-receptor  $\alpha$  function [110]. In addition to their localization in the nucleus, estrogen receptors also localize to the plasma membrane and discrete cytoplasmic organelles, such as the mitochondria and the endoplasmic reticulum. In these extranuclear locations, these receptors may mediate rapid nongenomic functions; for instance membrane-bound estrogen

receptors can associate with G protein leading to intracellular release of calcium, cyclic AMP generation, and kinase activation [111].

The connection between estrogen-receptor activity and diabetic nephropathy has emerged from clinical studies and animal studies, which have shown reduced levels of plasma estradiol and dysregulation of estrogen-receptor signaling in diabetic kidneys [112]. Premenopausal, nondiabetic women are known to have a reduced risk of renal disease compared with age-matched, nondiabetic men [112]. However, the presence of diabetes diminishes the protective effect of female gender so that diabetic women develop diabetic renal disease at levels generally equivalent to those of their diabetic male counterparts [113-114]. Numerous studies have suggested that estrogen receptors may have a role in the loss of female-sex renoprotection in patients with diabetes [112]. In support of this hypothesis, administration of estradiol or other selective modulators of the estrogen receptors has been found to attenuate the progression of diabetic nephropathy in patients with this condition and in animal models of the disease, as shown by the reduction of proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis. In the kidney, estrogen receptor signaling takes place in glomerular mesangial cells, endothelial cells, and podocytes. In these cells, estrogen receptor activation inhibits cell proliferation, decreases TGF- $\beta$  expression, decreases extracellular matrix accumulation, increases activity of endothelial nitric oxide synthase, and increases expression of VEGF [112, 115-116].

Additional studies are warranted to clarify the role of the estrogen receptors in the regulation of inflammation and lipid metabolism, and in the progression of diabetic nephropathy.

### **Estrogen-related receptors**

The ERR subfamily of orphan nuclear receptors consists of three members, ERR $\alpha$ , ERR $\beta$  and ERR $\gamma$ . Although these receptors are structurally homologous to estrogen receptors and bind estrogen response elements, they are not activated by estrogens and their physiological ligands are unknown. ERRs function as metabolic regulators in all aspects of energy homeostasis, including lipid and glucose metabolism and mitochondrial biogenesis [117]. All three ERRs are expressed at moderate-to-high levels in the kidney, but additional research is needed to determine the role of ERRs in this organ. The transcriptional control of energy homeostasis by ERRs strongly implicates their potential importance in slowing the progression of diabetic nephropathy. Agonists with increased relative selectivity for specific ERRs are becoming available and will help identify the function of specific ERR isoforms [117].

### **Summary**

The provided evidence suggests that several nuclear receptors especially the vitamin D receptor (VDR), farnesoid X receptor (FXR), and peroxisome-proliferator-associated receptors (PPARs) through their multiple actions in regulating lipid and energy metabolism, inflammation, oxidative stress and fibrosis exhibit a great potential in preventing the progression of diabetic nephropathy.

**(FIGURE ONE HERE)**

### **Acknowledgements**

The author thanks Jolene Richardson, Amber Leider, and Heidi Farmer for expert assistance in preparation of this review.

The original studies in this review are supported by grants from NIH (U01 DK076134 and R01 AG026529) and VA Merit Review.

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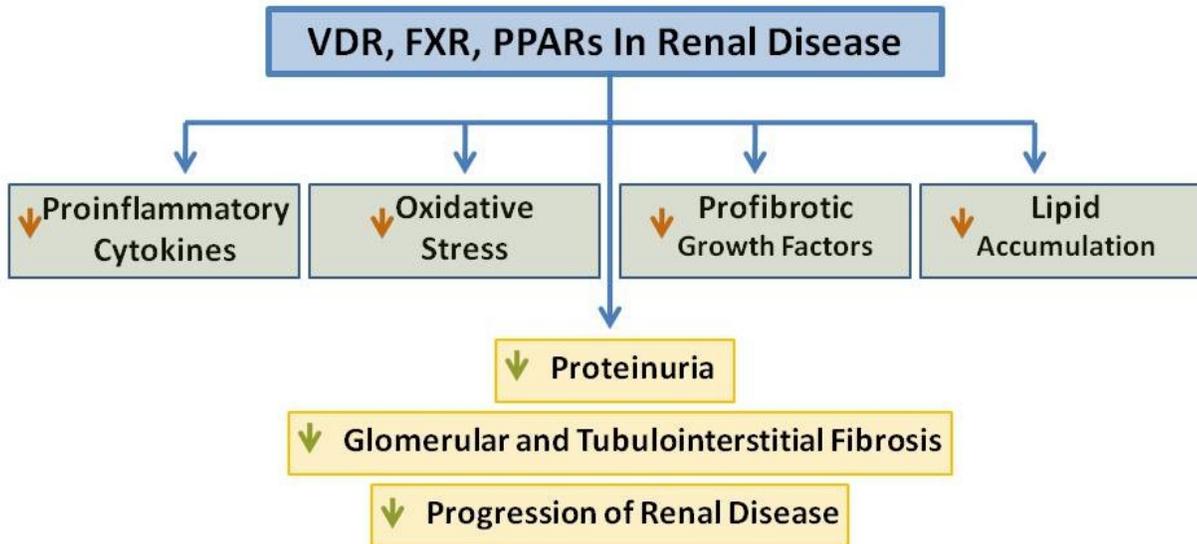
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Figure

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