# Lipoprotein Modification: A Hallmark in the Progression of Diabetic Nephropathy

*Corresponding Author:*
Dr. Viswanathan Pragasam,
Associate Professor, School of Bioscience and Technology, 632014 - India

*Submitting Author:*
Mr. Shiju M Thomas,
Senior Research Fellow(CSIR), School of Bioscience and Technology, VIT University, 103, Renal Research lab,
Centre for Biomedical Research, School of Bioscience and Technology, VIT University, 632014 - India

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***Author(s):*** Shiju TM, Pragasam V

## Abstract

Diabetic Nephropathy (DNP) is a chronic disease caused by diabetes that leads to end stage renal diseases. Although various pathological mechanisms have been proposed till date on the progression of DNP, the exact cause of this disease is still unknown. Here, we have focused on the modifications of low density lipoproteins (LDL) and its pathogenicity in DNP. LDL modification, specifically oxidation plays a major role in various disease states such as atherosclerosis, endothelial dysfunction, and cardiovascular diseases. However, its role in DNP is still unexplored. This review depicts the pathway in which LDL modification influences the development and perpetuation of DNP. Ox-LDL is taken up by the scavenger receptors such as CXCL-16 in podocytes and CD36 in tubular epithelial cells. This activates TGF-beta, which up-regulates the expression of matrix components such as collagen, fibronectin and laminin causing mesangial expansion and glomerulosclerosis. Simultaneously, there is an increased expression of VEGF and PDGF which could mediate macrophage infiltration and podocyte loss. This shows that Ox-LDL plays a major role in inducing the pathological changes in DNP.

## Introduction

Diabetes mellitus is a major metabolic disorder, affecting 200 million people across the world which is expected to rise up to 300 million by 2025 [1]. The leading cause of mortality in diabetic patients is through kidney damage caused by diabetic nephropathy (DNP). 'Prevention is better than cure' holds good for DNP because the best way of treatment for this disease is to control the risk factors such as increase in blood glucose and blood pressure level. However, in order to prevent a disease, the pathophysiology of the disease has to be well known. Various hypotheses have been proposed till date on how DNP progresses in human subjects. These include the involvement of renin- angiotensin system, advanced glycation end product formation (AGE), endothelial dysfunction, oxidative stress, and dyslipidemia (Illustration 1).

Lipids in general are used for energy storage by the living system. They also act as signaling molecules and structural components of the cell. Lipoproteins, which are composed of both lipids and proteins, are the transporters of lipids throughout the body. Of all the lipoproteins, low density lipoprotein (LDL) is called as 'Bad Cholesterol' because of its harmful effects; it becomes more dangerous when it is oxidized. The oxidized LDL (Ox-LDL) is implicated in the pathogenesis of various diseases such as atherosclerosis, cardiovascular diseases such as stroke, thrombosis, and endothelial dysfunction [2]. Apart from these diseases; it has also been found to be involved in the pathogenesis of DNP. However, the exact mechanism by which it mediates the progression of this disease is not fully known. In this study, we have depicted the mechanism by which modified LDL mediates different pathological changes in DNP.

## Review

**Lipoproteins**

Lipoproteins consist of both lipid and protein flocked together. The hydrophilic part of lipoprotein includes phospholipids, cholesterol, and apoprotein that are directed outwards, facilitates the transport of lipids around the body [3,4]. Lipoproteins are classified based on their size, density, and protein content as high density lipoproteins, low density lipoproteins, intermediate density lipoproteins, very low density lipoproteins, and chylomicrons. Of these, LDL is more harmful, less dense, with low protein content when compared to that of high density lipoprotein.

**Oxidation of LDL**

The LDL becomes treacherous when it is oxidized. The oxidation of LDL does not occur when they are in circulation because of the presence of anti-oxidant enzymes in the circulation [5]. However, oxidation takes place when a small portion of LDL that circulates in the plasma traverses the sub-endothelial space and gets engraved there [6]. The reason why and how this LDL reaches the sub-endothelial space is yet to be explored. In the sub-endothelial space, the LDL is more exposed to cellular derived oxidants and is less protected by antioxidants in circulation. The free radicals that are released from the

monocytes/macrophages, endothelial cells and smooth muscle cells oxidize LDL to form Ox-LDL. The in vitro oxidation of LDL has been performed by incubating LDL in the presence of transition metals,copper ions, and ozone [7]. Both the lipid and protein component of LDL are prone to modification during LDL oxidation. In 2001, Witztum et al. confirmed the oxidation of LDL and its pathogenicity in animal models [8]. Ox-LDL plays an important role in the development of dyslipidemia associated with the progression of chronic kidney diseases. Increase in the level of serum Ox-LDL was observed in patients with chronic kidney diseases, including nephropathy [9].

**Role of Oxidized LDL in Diabetic Nephropathy**

Oxidized LDL indirectly enhances the pathological changes in DNP by inducing the expression of Transforming Growth Factor- Beta (TGF-beta) [10]. Investigations carried out by Wrana et al. showed that oxidized LDL stimulates the expression of TGF-beta both in vivo and in vitro [11]. Activated TGF-beta is proven to show a direct role in the thickening of the glomerular basement membrane [12]. It binds to the TGF-beta type-II receptor that phosphorylates type-I receptor which results in the activation of Smad proteins [13]. This up-regulates the m-RNA and protein expression of extracellular matrix components such as collagen, fibronectin and laminin [14]. Also there is an increased level of protease inhibitors such as plasminogen activator inhibitor [15] and inhibitor of metalloproteinases [16]. Thus, the net result of TGF-beta activation is an increase in the synthesis of extracellular matrix proteins and a decrease in the degradation of extracellular matrix. This promotes the extracellular matrix accumulation which leads to glomerulosclerosis thereby contributing to DNP.

The pathways mediating the pathological changes in DNP by oxidized LDL are depicted in Illustration 2. TGF-beta inhibits the activity of cyclin-dependent kinases (CDK) by stimulating the expression of CDK inhibitors such as p27 and p21 [14]. Thus, the cells are arrested in the G1 phase with sustained protein synthesis that leads to cellular hypertrophy [17]. Also, TGF-beta enhances NOX-2 and NOX-4 (NADPH Oxidase isoforms) activity in kidney fibroblasts, which stimulates the mitogen pathway such as extracellular signal regulated pathway (ERK-1) [18]. This results in the conversion of fibroblast into myofibroblast that is associated with kidney fibrosis [19]. In podocytes, the Ox-LDL is up taken by the chemokine CXCL16, which is a membrane bound chemokine with solubilization property [20]. The podocytes that play a major role in the glomerular filtration is maintained by a complex of trans-membrane proteins of which nephrin plays the key role [21]. This nephrin expression is diminished by various circulating factors such as endothelin-1, and TGF-beta that are released from the mesangial cells [22]. This results in the podocyte loss with damage in the podocyte slit.

The uptake of Ox-LDL in podocytes induces the production of CXCL-12 which is a pro-inflammatory cytokine, whose biological effects are mediated by binding to the receptors CXCR4 and CXCR7 [23]. Increased expression of CXCL-12 and CXCR4 are observed in the distal as well as proximal tubule of the diabetic patients [24]. It was also evinced by Balabanian et al., that glomerulonephritis was prevented by blocking CXCL-12, and the activity was attributed to less podocyte proliferation and T-cell recruitment [25]. However, DNP is devoid of podocyte proliferation or autoimmunity and hence, the role of CXCL-12 in DNP is hardly predicted. But it can be speculated that the remodeling of glomerulus to glomerulosclerosis might be facilitated by CXCL-12 signaling [26].

In general, podocytes secrete vascular endothelial growth factor (VEGF) which is involved in maintaining the cellular polarity and the association of podocytes with mesangial cells [27]. Increase in the level of Ox-LDL is found to increase the level of VEGF expression and in turn this stimulates endothelial cells to synthesize (platelet derived growth factor) PDGF which further activates the mesangial cells. The activated mesangial cells secrete CCL2, ICAM and VCAM (Cell Adhesion Molecules) which are involved in the recruitment of monocytes into the glomerulus [28]. These recruited monocytes phagocytoze oxidized lipoproteins that lead to the formation of foam cells in the glomerulus. Activated monocytes mature into macrophages, which have been observed in the kidney biopsy sample of patients with diabetic nephropathy [29]. Thus, the pathological changes such as glomerulosclerosis, mesangial expansion, macrophage infiltration, cellular hypertrophy and podocyte loss are mediated by oxidized LDL.

**Glycation of LDL**

Glycation reaction is a sequence of events, which is initiated by the interaction between free glucose and the amino group of protein. This proceeds to a labile Schiff-base that rearranges to form amadori product. This amadori product is considered to be the stable form of glycated protein [30]. All proteins are subjected to glycation when they are exposed to glucose moieties of which there is no exception [31]. Incubation of LDL with glucose at pharmacological concentration in vitro resulted in the glycation of apo-B

protein present in LDL. The extent of glycation is found to be directly proportional to the concentration of glucose present [32]. The same was observed in vivo in which the level of glycated apo-B correlated with the average level of plasma glucose. A 33-fold increase in the level of glycated apo-B has been reported in diabetic patients compared to normal subjects [33].

**Role of glycated LDL in DNP**

The pathogenesis of glomerulosclerosis resembles that of atherosclerosis, which led to the speculation that lipids when modified play a critical role in the progression of DNP. In the early stages of DNP, LDL gets trapped in the sub-endothelial space. Because of the increased level of glucose in diabetic patients, they are easily glycated and these glycated LDL are more prone to oxidation compared to native LDL [34]. The glycoxidated LDL is highly reactive and cause damage to the kidney directly. Simultaneously when more glycated and oxidized LDL are formed, there is an increase in the expression of scavenger receptors in the mesangial cells which are responsible for the uptake of these modified LDL. This results in the mesangial matrix expansion that leads to glomerulosclerosis. The glycoxidated LDL is also up taken by the scavenger receptor CD36 that are localized on the proximal tubular epithelial cells. Increase in the level of modified LDL has been proven to increase the CD36 expression through PPAR-beta activation. The uptake of glycoxidated LDL induces Serine/Threonine kinases which further activate mitogen activated protein kinases. This results in the activation of caspases which leads to the apoptosis of proximal tubular cells exacerbating the kidney damage [35].

Alternatively, hyperglycemia facilitates the glycation of proteins of which megalin and cubulin are of no exception [36]. These proteins that are present in the tubular membrane are responsible for the reabsorption of low and high molecular weight proteins. Cubulin with a molecular weight of 460 kDa is the receptor for large molecules that are present in the glomerular filtrate such as lipoproteins (apo-A, apo-B, oxidized LDL, HDL) and transferrin [37]. When cubulin is glycated, there is no reabsorption of these lipoproteins that leads to the accumulation of proteins in the glomerular filtrate. The presence of high molecular proteins in the glomerular filtrate stimulates the secretion of cytokines by tubular epithelial cells that results in interstitial fibrosis [38].Gekle et al. showed that increase in TGF-beta expression has a direct role in reducing the expression of megalin, which is an albumin binding receptor protein thus, reducing the albumin uptake [38]. This confirms the direct role of TGF-beta in the induction of albuminuria in diabetic patients [39].

**Substantiation of the mechanism by various drugs**

In diabetic patients with chronic kidney diseases there is an increased production and decreased catabolism of LDL cholesterol, which ultimately results in an increase in the total and LDL cholesterol level [40]. This shows that hyperlipidemia could aggravate DNP by altering fibrinolytic system and damaging endothelial cells [41]. So, it was speculated that any drug that could ameliorate dyslipidemia would be a better drug for the treatment of chronic kidney diseases.

Metformin, an aminoguanidine derivative is being used as an insulin sensitizing agent and it has the ability to attenuate hyperglycemia [42]. It could also prevent the formation of AGE products [43] and decrease the lipid profile in diabetic patients.It modulates the genes responsible for oxidative stress and improves microalbuminuria, thus attenuating diabetic nephropathy [44]. Likewise, few investigations on NADPH oxidase inhibitors (apocynin and diphenylene iodonium) proved that these drugs reducing renal ROS generation, has the ability to decrease VEGF expression, chemokine secretion and macrophage infiltration [45]. Thus they could ameliorate mesangial matrix expansion and attenuate diabetic nephropathy. Thiazolidinedione drugs are a group of drugs that belong to insulin sensitizers and are aimed to target peroxisome proliferator activated receptor- gamma (PPAR-beta) receptors. Unsaturated fatty acids are up-taken by these PPAR-beta receptors which play a vital role in lipid metabolism and adipogenesis. They are expressed in monocytes and macrophages that are present in liver, skeletal muscle, and kidney [46]. These drugs decrease the expression of fibronectin induced by TGF-beta in mesangial cells and also decrease ERK-1 expression thus reducing glomerular hyperfiltration and albuminuria in STZ induced diabetic rats [47]. It improves cellular hypertrophy and extracellular matrix accumulation by preventing the G1 phase cell cycle arrest which is prominent in causing DNP [48]. Though the drugs that were identified are not able to cure the chronic kidney diseases, they could improve dyslipidemia and thus could postpone the progression of kidney damage.

Statins, apart from its lipid lowering activity, has a great potential in ameliorating diabetic nephropathy. Administration of statins inhibits the proliferation of mesangial cells thus inhibiting the activation of TGF-beta and accumulation of macrophages [49]. Similarly, clofibrate a lipid lowering drug that reduces TGF-beta expression is found to improve albuminuria

[50]. The direct supplementation of fatty acids such as fish oil, omega-3 fatty acids have also improved tubulointerstitial fibrosis in rats [51]. Pravastatin at a dosage of 10 mg [52] and atorvastatin [53] at varying doses showed 50% reduction in the urinary protein excretion. In a similar study, it was found that pravastatin is effective when the GFR is less than 40ml/min per 1.73m2 and has no effect when the GFR is more than 60 ml/min per m2 [54]. This finding puzzled all researchers and the clarification was given by Spencer et al. that hyperlipidemia and hyperglycemia act synergistically to induce DNP and it was confirmed in LDL-receptor deficient mice [55]. This shows that in future any treatment strategies that are targeted towards the progression of DNP should target both hyperlipidemia and hyperglycemia.

To recap, DNP is a multifactorial disease which is clearly evident from the number of hypothetical mechanisms that have been proposed till date. These pathways lead to DNP at different intervals that depend on the individual's blood glucose level, blood pressure, race, and heredity. In addition to all these causatives, it has been proven already that dyslipidemia also plays a role in DNP. However, the exact mechanism how it mediates the progression is not known. In this review, we have discussed the possible mechanism by which both oxidized and glycated LDL lead to diabetic nephropathy. We are working on the treatment strategies targeting this pathway which would prevent or at least delay the progression of DNP.

## Conclusion

To conclude, though various drugs have been identified to treat DNP the incidence of this disease is increasing every year. The main problem with DNP is that the disease can be diagnosed only at a stage when nothing could be done to prevent the progression. So any treatment strategies that are designed to target this disease should be able to arrest the progression of the disease at an early stage. In order to prevent the progression of the disease the pathophysiology of the disease has to be well known. Here we have shown the mechanism how the modified lipoproteins play a major role in mediating DNP. Understanding the mechanism would be helpful in the future to completely prevent the disease.

## Abbreviation(s)

RAS: Renin- Angiotensin System;

AGE: Advanced Glycation End products;
PKC: Protein Kinase C;
MAPK: Mitogen Activated Protein Kinase;
TGF-?: Transforming Growth Factor-beta;
PDGF: Platelet- Derived Growth Factor;
VEGF: Vascular Endothelial Growth Factor,
PDGF: Platelet- Derived Growth Factor;
CDk: Cyclin Dependent kinase;
ERK-1: Extracellular signal Regulated Kinase;
PAI-1: Plasminogen Activator Inhibitor;
TIMP: Tissue Inhibitor of Metalloproteinases
NOX2, NOX4: NADPH Oxidase isoforms
ECM: Extracellular Matrix.

## Acknowledgement(s)

## References

1. Wild S, Roglic W, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2000; 27:1047-53.

2. Esterbauer H, Jurgens G, Quenhenberger O, Koller E. Autoxidation of human low density lipoprotein: loss of polyunsaturated fatty acids and vitamin E generation of aldehydes. J Lipid Res 1987; 28: 595-609.

3. Fahy E, Subramaniam S, Brown HA. A comprehensive classification system for lipids. J Lipid Res 2005; 46; 5: 839-61.

4. Segrest JP, Jones MK, Deloof H, Dashti N. Structure of apolipoprotein B-100 in low density lipoproteins. J Lipid Res 2001; 42: 1346-67.

5. Frei B, Stocker R, Ames BN. Antioxidant defenses and lipid peroxidation in human blood plasma Proc Natl Acad Sci 1988; 85: 9748-52.

6. Schwenke DC, Carew TE. Initiation of atherosclerotic lesion in cholesterol fed rabbits; Selective retention of LDL vs. selective increases in LDL permeability in susceptible sites of arteries. Arteriosclerosis 1989; 9: 908-18.

7. Brown AJ, Dean RT, Jessup W. Free and esterified oxysterol: formation during copper-oxidation of low density lipoprotein and uptake by macrophages. J Lipid Res 1996; 37: 320-35.

8. Witztum JL, Steinberg D. The oxidative modification hypothesis of atherosclerosis: does it hold for humans?

Trends Cardiovascul Med 2001; 11: 93-102.

9. Kasahara J, Kobayashi K, maeshima Y, Yamasaki Y, Yasuda T, Matsuura E, Makino H. Clinical significance of serum oxidised low density lipoprotein/?2-glycoprotein complexes in patients with chronic renal diseases. Nephron Clin Pract 2004; 98: c15-c24.

10. Nakhjavani M, Esteghamati A, Deh OK, Asgarani F, Mansoumia N, Abbasi M. Association of macroalbuminuria with oxidized LDL and TGF-b in type 2 diabetic patients: a case control study. Int Urol Nephrol 2010; 42: 487-92.

11. Wrana JL, Attisano L, Wieser R. Mechanism of activation of TGF-? receptor. Nature 1994; 370: 341-347

12. Rutledge JC, Ng KF, Hnin A, Wilson DW. Role of triglyceride- rich lipoproteins in diabetic nephropathy. Nature Rev Nephrol 2010; 6: 361-70.

13. Wrana JL, Attisano L, Wieser R. Mechanism of activation of TGF-? receptor. Nature 1994; 370: 341-47

14. Chen S, Hong SW, Iglesias-de La Cruz MC. The key role of the transforming growth factor beta system in the pathogenesis of diabetic nephropathy. Ren Fail 2001; 23: 471-81.

15. Wilson HM, Reid FJ, Brown PAJ. Effect of transforming growth factor- b1 on plasminogen activator inhibitor type-1 in glomerular cells. Exp Nephrol 1993; 1: 343-50.

16. Choi ME. Mechanism of transforming growth factor- beta1 signaling: role of mitogen activated protein kinase. Kidney Int 2000; 58: S53-S58.

17. Van den berg BM, Vink H, Spaan JA. The endothelial glycocalyx protects against myocardial edema. Circ Res 2003; 92:592-94.

18. Constant Inescu AA, Vink H, Spaan JA. Endothelial cell glycocalyx modulates immobiisation of leukocytes at the endothelial surface. Arterioscler Thromb Vasc Biol 2003; 23: 1541-47.

19. Bondi CD, Nagaraj M, Duck YL, Karen B, Yves G, Hanna AA, Jeffrey LB. NADPH oxidase mediates TGF-beta1 induced activation of kidney myofibroblasts. J Am Soc Nephrol 2010; 21: 93-102.

20. Nosadini R, Tonolo G. Role of oxidized low density lipoproteins and free fatty acids in the pathogenesis of glomerulopathy and tubulointerstitial lesions in type 2 diabetes. Nutr Metab Cardiovasc Dis 2011; 21: 79-85.

21. Endlich K, Kriz M, Witzgall R. Update in podocyte biology. Curr Opin Nephrol Hypertens 2001; 10: 331-40.

22. Hauser PV, Collino F, Bussolati B, Camussi G. Nephrin and endothelial injury. Curr Opin Nephrol Hypertens 2009; 18: 3-8.

23. Burns JM, Summers BC, Wang Y. A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development. J Exp Med 2006; 203: 2201-13.

24. Lotan D, Sheinberg N, Kopolovic J, Dekel B. Expression of SDF-1/CXCR4 in injured human kidneys. Pediatr Nephrol 2008; 23: 71-77.

25. Balabanian K, Couderc J, Bouchet-Delbos L. Role of the chemokine stromal cell-derived factor 1 in autoantibody production and nephritis in murine lupus. J Immunol 2003; 170: 3392-400.

26. Sufyan G.S. Role of pro-inflammatory and homeostatic chemokines in diabetic nephropathy. Submitted as dissertation. 2010.

27. Hakroush S. Effects of increased renal tubular vascular endothelial growth factor on fibrosis, cyst formation and glomerular disease. Am J Pathol 2009; 175: 1883-95.

28. Grone HJ, Walli AK, Grone EF. The role of oxidatively modified lipoproteins in lipid nephropathy. Contrib Nephrol 1997; 120: 160-75.

29. Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. Diabetes Metab 2000; 26: 254-64.

30. Kyons TJ. Glycation, Oxidation, and glycoxidation reactions in the development of diabetic complications, In: Maeda K, Shinzato T (ed). Dialysis related amyloidosis control nephrol Basel: Karger 1995; 112: 1-10.

31. Baynes J. Role of oxidative stress in the development of complications in diabetes. Diabetes 1991; 40: 405-11.

32. Schleicher E, Deufel T, Wieland OH. Non-enzymatic glycation of human serum lipoproteins. Elevated epsilonlysine glycosylated low-density lipoprotein in diabetic patients. FEBS Lett 1981; 129: 1-7.

33. Kyons TJ, Baynes JW, Patric JS, Colwell JA. Glycosylation of low density lipoprotein in patients with type-1 diabetes: correlation with other parameters of glycemic control. Diabetologia 1986; 29: 685-91.

34. Sobal G, Menzel J, Sinzinger H. Why is glycated LDL more sensitive to oxidation that native LDL? A comparative study. Prostaglandins Leukot Essent Fatty Acids 2000; 63; 4: 177-86.

35. Katalin S, Emilio C, Peter M, Kumar S, Erwin PB. Multiple metabolic hits converge on CD36 as novel mediator of Tubular Epithelial Apoptosis in Diabetic nephropathy. PLoS Med 2005; 2: 152-61.

36. Steibercher UP, Witztum JL. Glycosylation of low density lipoprotein to an extent comparable to that seen in diabetes slows their catabolism. Diabetes 1984; 33: 130-34.

37. Verroust PJ, Christensen EI. Megalin and Cubulin-

the story of two multipurpose receptors unfolds. Nephrol Dial Transplant 2002; 17: 1867-71.

38. Gekle M, Knaus P, Neilsen R. Transforming growth factor beta 1 reduces megalin and cubulin mediated endocytosis of albumin in proximal derived opossum kidney cells. J Physiol 2003; 552: 471-81.

39. Russo LM, Osicka TM, Brammar GC, Candido R, Jerums G, Comper WD. Renal processing of albumin in diabetes and hypertension in rats: possible role of TGF-beta 1. Am J Nephrol 2003; 23: 61-70.

40. Farbakhsh K, Kasiske BL. Dyslipidemias in patients who have chronic kidney disease. Med Clin North Am 2005; 89: 689-99.

41. Misra A, Kumar S, Vikram NK, Kumar A. The role of lipids in the development of diabetic microvascular complications: Implication of therapy. Am J Cardiovasc Drugs 2003; 3: 325-38.

42. Fanghanel G, Sanchez-Reyes, Trujillo C, Sotres D, Espinosa-Campos J. Metformins effects on glucose and lipid metabolism in patients with secondary failure to sulfonylureas. Diabetes Care 1996; 19: 1185-89.

43. Ruggiero-Lopez D, Lecomte M, Moinet G, Patereau G, Lagarde M, Wiernsperger N. Reaction of metformin with dicarbonyl compounds. Possible implication in the inhibition of advanced glycation end product formation. Biochem Pharmacol 1999; 58: 1765-73.

44. Bolen S, Feldman L, Vassy J. Systematic review: comparative effectiveness and safety of oral medications of type 2 diabetes mellitus. Ann Intern Med 2007; 147: 386-99

45. Kensuke A, Akihiro T, Maristela LO, Atsuo G, Mark TQ, Toshiro F, Christopher SW. Effects of NADPH oxidase inhibitor in diabetic nephropathy. Kidney Int 2005; 67: 1890-1898.

46. Blanquart C, Barbier O, Fruchart JC, Stales B, Glineur C. Peroxisome proliferator-activated receptors: regulation of transcriptional activities and roles in inflammation J Steroid Biochem Mol Biol 2003; 85: 267-73.

47. Isshiki K, Haneda M, Koya D, Maeda S, Sugimoto T, Kikkawa R. Thiazolidinedione compounds ameliorate glomerular dysfunction independent of their insulin-sensitizing action in diabetic rats. Diabetes 2000; 49: 1022-32.

48. Griffin SV, Pichler R, Wada T, Vaughan M, Durvasula R, Shankland SJ. The role of cell cycle proteins in glomerular disease. Sem Nephrol 2003; 23: 569-82.

49. Massy ZA, Ma JZ, Louis TA, Kasike BL. Lipid lowering therapy in patients with renal disease. Kidney Int 1995; 48: 188-98.

50. Luo P. Glomerular 20-HETE, EEts, and TGF-b in diabetic nephropathy. Am J Physiol 2009; 286: F556-563

51. An WS, kim HJ, Cho KH, Vaziri ND. Omega-3 fatty acid supplementation attenuates oxidative stress, inflammation and tubulointerstitial fibrosis in the remnant kidney. Am J Physiol Renal physiol 2009; 297: F895-903.

52. Lee TM, Su SF, Tsai CH. Effect of pravastatin on patients with well controlled hypertension. Hypertension 2002; 40: 67-73.

53. Bianchi S, Bigazzi R, Caiazza A, Campese VM. A controlled prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. Am J Kidney Dis 2003; 41: 565-70.

54. Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC. For the cholesterol and Recurrent Events (CARE) Trial investigators: Effect of Pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. J Am Soc Nephrol 2003; 14: 1605-13.

55. Spencer MW, Muhlfeld AS, Sererer S. Hyperglycemia and Hyperlipidemia act synergistically to induce renal disease in LDL-receptor deficient BALB mice. Am J Nephrol 2004; 24: 20-31.

# Illustrations

## Illustration 1

Illustration 1: Pathway mediating the progression of diabetic nephropathy from diabetes The figure shows the factors that are involved in the progression of diabetic nephropathy. The factors such as renin-angiotensin system, advanced glycation end product formation, and oxidative stress converge at a single point; activating the PKC/MAPK pathway. Activated PKC is involved in the pathogenesis of DNP.
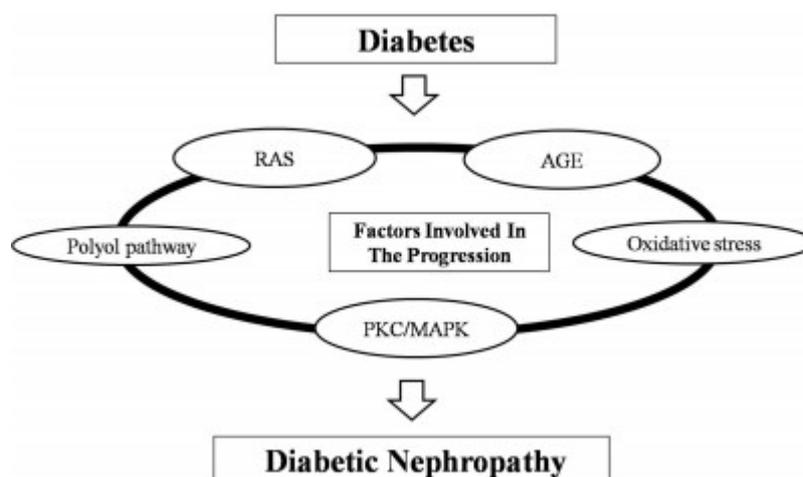


## Illustration 2

Illustration 2: Pathway depicting the progression of different pathological changes in diabetic nephropathy mediated by oxidized LDL. Oxidation of LDL results in an increase in the expression of TGF-β. Activated TGF-β mediates the pathways leading to the pathological changes such as glomerulosclerosis, podocyte loss, interstitial fibrosis, cellular hypertrophy, macrophage infiltration.
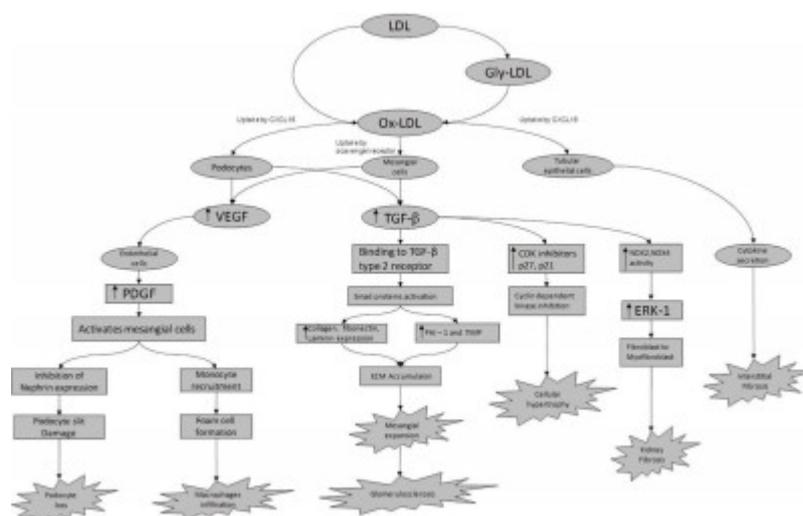
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