

Original Review Article

# Role of cytokines IL-1, IL-6 and TNF- $\alpha$ in the pathogenesis of diabetic nephropathy

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## Abstract

Diabetes mellitus is associated with various biochemical alteration including glucose and lipid peroxidation, and diabetic nephropathy (DN) develop as its complication in 20-40% patients of type 2 diabetic. Hemodynamic and metabolic changes are the main bases of DN pathogenesis. However, inflammation plays the main role in DN pathophysiology. Pro-inflammatory cytokines mainly tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 1 (IL-1) and interleukin 6 (IL-6), are known to be involved among several inflammatory molecules. AGE (Advanced glycation end products) and PKC (protein kinase C) pathways are activated by hyperglycemia. Activation of this pathways lead to pro-inflammatory cytokines generation. Development of DN take place due to signaling pathway initiated by pro-inflammatory cytokines that lead to extracellular matrix (ECM) accumulation, glomerular basement membrane (GBM) thickening, and glomerulosclerosis. By knowing these signaling pathways novel therapeutic approach can be developed for development of better treatment modality of DN. In this field for future research the detail knowledge of this mechanism will also be useful.

## Key words

Pro-inflammatory cytokines, Interleukin 1 (IL-1), Interleukin 6 (IL-6), Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), Inflammatory cytokines, Renal Diseases.

## Introduction

One of a group of chronic disorders related to metabolism is Diabetes Mellitus with high sugar levels in blood along with disturbances of fat, protein and carbohydrate, metabolism result from defects in insulin secretion and action [1].

In India, a huge caseload of diabetes mellitus type 2 (DM), about 69.9 million Indians are supposed to affect by the year 2025 [2]. The diabetes mellitus consequences include long-term failure of various organs along with damage and dysfunction [3]. The Diabetes mellitus induce microvascular problems which in turn lead to blindness, renal failure and nerve damage [4]. Diabetic nephropathy is one of a high morbidity and mortality disorder which incidence and prevalence rate is increasing [5]. End-stage renal disease (ESRD) causes DN in 20-40% of people with type 2 DM [6, 7, 8]. The onset of symptoms is 5 to 10 years after the disease begins [9]. Late symptoms are frequent urination at night: nocturia. Some other symptoms are nausea, vomiting, headaches, lack of appetite, tiredness, frequent daytime urination, swelling of leg and itching of skin [9]. Inflammatory cytokines are involve in DN is still not clear, in this review pathways of inflammatory cytokines and their role in DN is elaborated.

## Pathogenesis

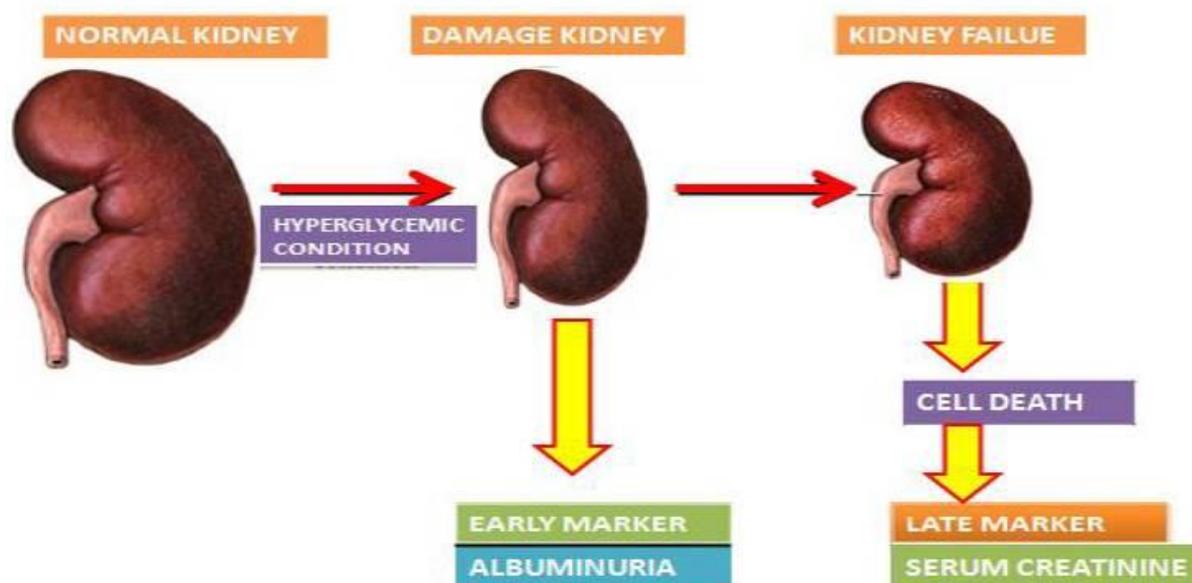
Genetic and some environmental factors trigger Pathogenesis of DN. In pathomechanism of DN hyperglycemia cause metabolic, hemodynamic

and molecular changes too [10, 11]. Researcher came to know that now a days in progression of DN, immunological and inflammatory factors play important role by conducting intensive research at cellular and molecular level [12, 13]. In DN development, there are implication of various cells like macrophages, leucocytes (peripheral total and differential), monocytes and nuclear factor (NF-kB) [14, 15]. Intracellular adhesion molecule-1 (ICAM-1) is adhesion molecules, chemokines, growth factors and enzyme. Growth factors like vascular endothelial growth factors (VEGF), growth hormone (GH), and insulin-like growth factor (IGF) are also involve [16, 17]. Since, information regarding the role of inflammatory cytokines in DN development and progression is still lacking. To find novel therapeutic strategies, to prevent DN development to extend the knowledge regarding the role of inflammation is useful. Early kidney changes and its biomarker Hypertrophy and hyperfiltration are significant changes in DN. These changes are associated with inflammatory processes, particularly pro-inflammatory cytokines [18, 19]. Renal distal tubule have epithelial sodium channel through which TNF- $\alpha$  intensifies the reabsorption of sodium by activating it which in turn leading to renal hypertrophy and subsequently triggers the release of TGF- $\beta$  [20]. In diabetic patients there is involvement of renal. Proteinuria with elevated GFR but not an alteration of serum creatinine is the earliest changes in the kidney of diabetic (Table – 1/ Figure - 1) [21].

**Table – 1:** Classification of glomerular filtration rate (GFR) in CKD Category Glomerular filtration rate (GFR) [26].

Category	Glomerular filtration rate (GFR) (mL/min/1.73m <sup>2</sup> )
G1 (normal or high)	$\geq 90$ G2
G2 (slightly decreased)	60-89
G3a (slight or moderately decreased)	45-59
G3b (moderately-to-severely decreased)	30-44
G4 (severely decreased)	15-29
G5 (renal insufficiency)	<15

**Figure - 1:** Early kidney changes and its biomarker.



**Table – 2:** Classification of albuminuria in CKD [26].

Category	AER		
	(mg/24h)	(mg/ mmol)	(mg/g)
A1 (normal to slightly elevated)	<30	<3	<30
A2 (moderately elevated)	30 -300	3 - 30	30 – 300
A3 (severely elevated)	>300	>30	>300

Estimated glomerular filtration rate (e GFR) and albuminuria are two diagnostic modalities involve in Identifying and monitoring DN. Sensitive marker of various kidney diseases VCD and chronic kidney disease (CKD) is albuminuria. Chronic kidney disease defined as an abnormality of kidney structure and function for > 3 months accompanied with structural damage that proved histologically. In normal kidney function without albuminuria GFR of =90 mL/min/1.73 m<sup>2</sup> is seen. To calculate e GFR Equation from Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification on Diet in Renal Disease (MDRD) is used [22, 23]. There are 5 categories of GFR function (**Table – 2/ Figure - 2**), while albuminuria classified into 3 categories (**Figure – 3**) [24]. In diabetic patients the decrease in GFR and albuminuria of > 300 mg/day are significant marker to indicate the presence or development DN [25].

#### Cytokines involve in diabetic nephropathy

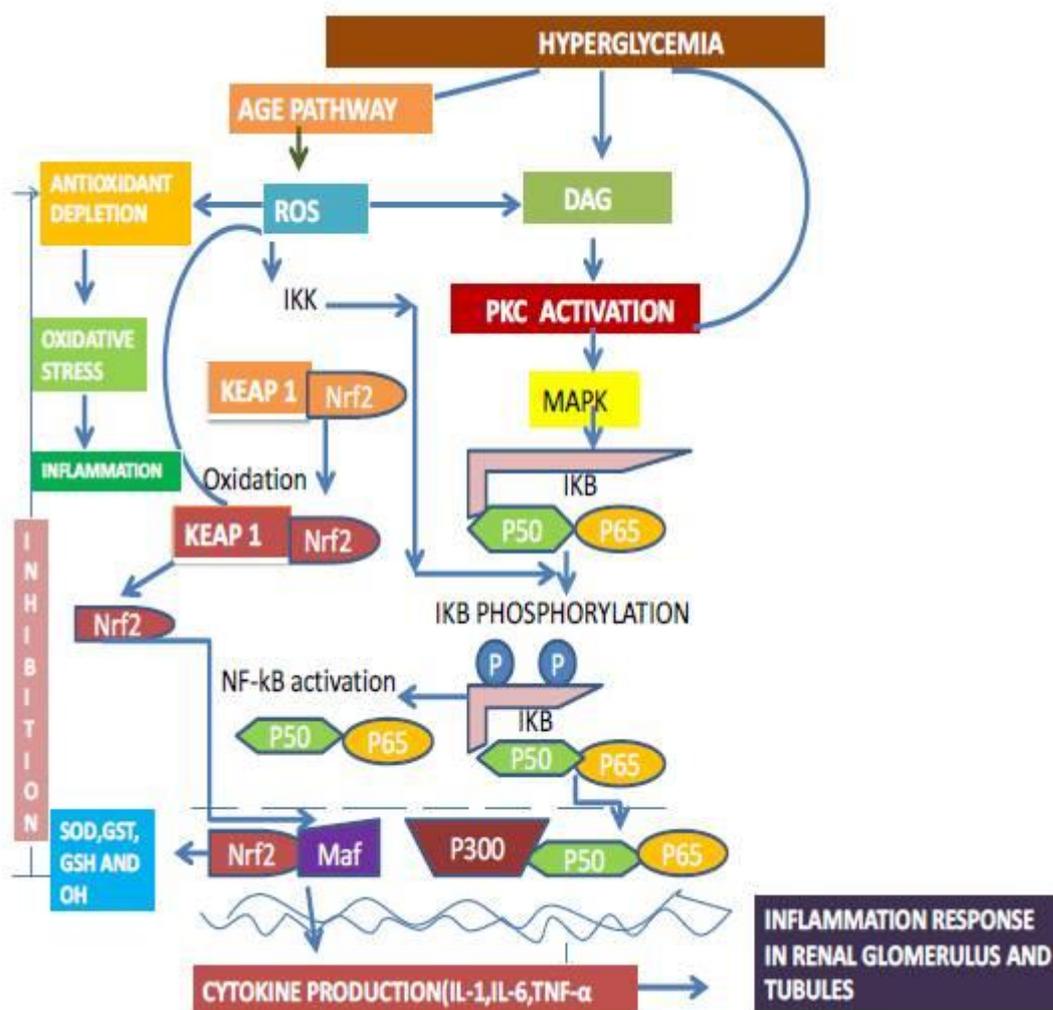
In the pathogenesis of DN inflammatory response play the important role for the first time was demonstrated by Hasegawa, et al. [26]. DM is characterized by hyperglycemia that lead to, formation of certain pro-inflammatory cytokines by activating numerous metabolic pathways like; AGE (advanced glycation end products) and PKC (Protein kinase c) pathway which in turn cause renal damage, either glomerulus or other structures like tubular renal cells, endothelial, mesangial, and epithelial cells by producing various AGE products.

In AGE pathway, ROS (reactive oxygen system) production is initiated and amplified in chronic hyperglycemic condition and cause oxidative stress due depletion of antioxidants. It may also result in, tissue injury, activation of nuclear factor (erythroid-1) related factor (Nrf2), and activation of inhibitory kappa B kinase (IKK). Oxidation of thiol residues on kelch-like ECH

associated protein-1 (Keap-1) cause activation of Nrf2. Nrf2 enter the nucleus and bind to antioxidant response element (ARE) on genome, activate ARE which in turn produce many cytoprotective and antioxidants enzymes such as superoxide dismutase (SOD), glutathione (GSH), heme oxygenase (HO-1), and glutathione s-transferase and protect a cell from an elevation of oxidative stress, thus prevent inflammation. However, diabetic condition lead to hyperglycemic in this condition cellular homeostatic function is impaired and inflammation occurred because in hyperglycemic

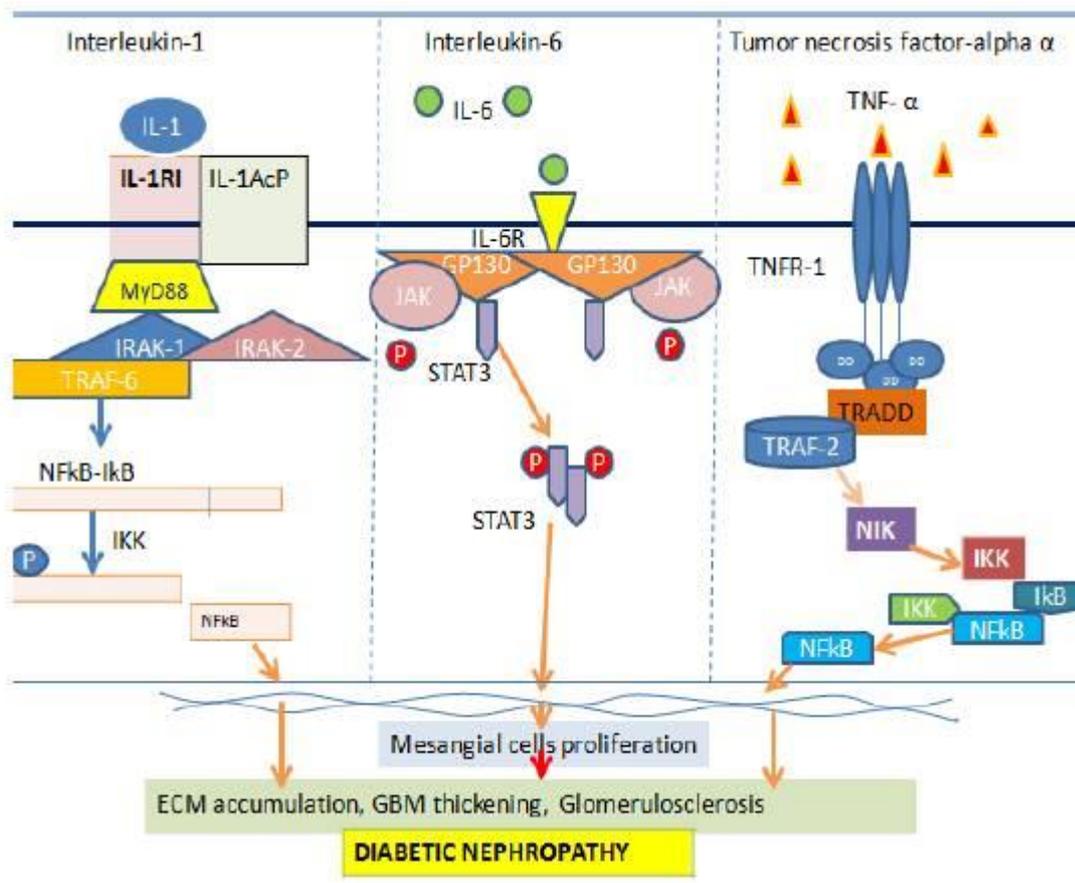
condition activation of Nrf2 is inhibited by activation of the extracellular related kinase (ERK) [27, 28]. Hyperglycemia also activates PKC and up regulates MAPK signaling pathway. ROS activation of IKK induces phosphorylation of inhibitory kappa B protein (I $\kappa$ B). Phosphorylation of I $\kappa$ B releases free NF- $\kappa$ B heterodimer from I $\kappa$ B via ubiquitination and proteasomal degradation, free NF- $\kappa$ B enter into the nucleus and bind with kappa region of genome increasing production of cytokines [29, 30].

**Figure - 2:** Hyperglycemia-induced production of pro inflammatory cytokine in the pathogenesis of DN.



**Footnote-** PKC: Protein Kinase c; AGE: Advanced Glycation End products; ROS: ReactiveOxygen Species; Nrf2: Nuclear Factor (erythroid-1) related factor; IKK: Iinhibitory Kappa B Kinase; SOD: Super Oxide Dismutase; GSH: Glutathione Rreductase; HO-1: Heam Oxygenase; GST: Glutathione S Ttransferase; ERK: extracellular related kinase; NF-kb: Nuclear Factor Kappa Light – Chain Enhancer Of Activated B Cells.

**Figure - 3:** IL-1, IL-6, and TNF- $\alpha$  signaling mechanism in relation to diabetic nephropathy.



**Footnote-** IL-1: Interleukin – 1; IL-1RAcP: Interleukin Receptor Accessory Protein; MYD88: myeloid differentiation factor-88; IRAK: IL receptor-associated kinase; TRAF: TNF receptor-associated factor; NF-kb: Nuclear Factor Kappa Light – Chain Enhancer Of Activated B Cells; IKK: Inhibitory kappa B kinase; NIK: NF-kB-inducing kinase; JAK: Janus kinase; STAT: signal transducer and activator of transcription; DD: Death Domain; TRADD: TNF receptor-associated death domain.

### Interleukin 1 (IL-1)

Interleukin 1 is proinflammatory cytokines which is involved in inflammation-based disease e.g. sepsis, autoimmune disease, even in DN too. It is of two types IL-1 $\alpha$  and IL-1 $\beta$  [31]. It is produced primarily by macrophage, but lymphoid, epidermal, vascular, and epithelial tissues also synthesize IL-1 and also synthesis by renal cells, i.e. tubular, endothelial, mesangial, and epithelial cells are also capable of producing IL-1, which interact with other cytokines and can act as either autocrine or paracrine to inflict renal damage; hence involved in several renal diseases, including DN [32, 33]. The IL-1 release through cell lysis, secretory lysosomes, and microvesicle shedding, binds to its receptor IL-1RI, alongside IL-1 receptor accessory protein (IL-1RAcP), as

ligand bind to its receptor initiates signaling transduction, which includes myeloid differentiation primary response protein 88 (MyD88), IL-1 receptor-associate kinase (IRAK-1) and IRAK-2, then lead to recruitment of TNF receptor-associated factor 6 (TRAF-6) and activation of nuclear factor kappa B (NF-kB) and from complex with I $\kappa$ B [34]. Subsequently, NF-kB migrate into the nucleus and bind with the genome, and various events occur, that is an accumulation of extracellular matrix, ultimately lead to glomerulosclerosis [35].

### Interleukin 6 (IL-6)

Sekizuka, et al. suggested that pro-inflammatory cytokines play role in the pathological mechanism of DN [36]. Two functional

membrane proteins 80 kDa ligand-binding IL-6R and 130 kDa signal-transducing chain gp130 are involved in the signalling mechanism mediated by IL-6. IL-6 activates these receptors which in turn lead to transphosphorylation and activation of JAKs. This causes phosphorylation of gp130 tails which in turn recruits STAT3 proteins. Phosphorylated STAT3 enters into the nucleus and subsequently, enhances transcription of many genes [37]. Thus IL-6 promotes growth and proliferation of mesangial cells [38]. Activated mesangial cells cause accumulation of extracellular matrix (ECM), glomerular basement membrane (GBM) thickening, and glomerulosclerosis, ultimately leading to diabetic kidney disease [39, 40].

#### **TNF - $\alpha$ (Tumor necrosis factor - $\alpha$ )**

TNF- $\alpha$  is an inflammatory cytokine which can affect the activity of multiple cells like, apoptotic and necrotic cells either directly or by autocrine mechanism. TNF- $\alpha$  increases albumin permeability by hampering the function of the barrier glomerular capillary wall. TNF- $\alpha$  is synthesized by hematopoietic cells, e.g. monocytes, macrophages, and T cells, and also by intrinsic renal cells, e.g. mesangial, endothelial, dendritic, and renal tubular cells [41-46]. There are two receptors (TNFR-1 and TNFR-2) via which TNF- $\alpha$  acts and plays its role in DN. The affinity of TNFR-1 is five times less than TNFR-2, but TNFR-1 is expressed in all types of cells and plays its role in many biological activities, while TNFR-2 action is limited to immune cells only.

The main function of TNF- $\alpha$  in signaling pathway is to activate NF- $\kappa$ B which subsequently enters the nucleus and binds to its genome. As NF- $\kappa$ B binds to its genome it leads to an accumulation of extracellular matrix and glomerulosclerosis. All this is a chain reaction as TNF- $\alpha$  binds to TNFR-1 resulting in TNFR-associated death domain (TRADD) binding to the death domain (DD) of TNFR-1 and recruiting TNFR-associated factor 2 (TRAF-2). This adaptor protein recruits NF- $\kappa$ B-inducing kinase (NIK) and IKK complex, which activates NF- $\kappa$ B

and so on [47].

#### **Futuristic scope of these cytokines in DN**

Still there is no effective way to intervene the signaling pathway involved in development of DN in DM subjects and therefore there is a lack of effective treatment to prevent the development of DN. Regulation of blood glucose and lipid profile levels are still the main treatment modalities [48]. Unfortunately, these approaches can't protect the kidney completely from injury. Therefore, still, there is a need for novel therapeutic strategies that can intervene the major pathophysiological mechanism of DN. Regulation of TNF- $\alpha$  may reduce the progressivity of renal damage in diabetic conditions. Doherty et al. worked on pentoxifylline (PTF), it is a methylxanthine-derived phosphodiesterase inhibitor and has anti-inflammatory properties. Doherty et al. came to the conclusion that inhibition of TNF- $\alpha$  may be used as a treatment modality to intervene DN development by reducing urinary protein excretion in patients with diabetes, both in normal renal function or insufficiency [49-52]. PTF acts by decreasing the levels of TNF- $\alpha$  and thus inhibits the urinary protein accumulation without any metabolic or hemodynamic change. Besides its effect on TNF- $\alpha$ , in the inflammatory response like, activation, adhesion, and phagocytosis, PTF attenuates cellular processes without any haemodynamic or metabolic change and it also has a considerable capacity to modulate other proinflammatory cytokines and molecules, including IL-10, IL-6, and IL-1 $\beta$  [53, 54]. Another study with Infliximab is a chimeric anti-TNF- $\alpha$  antibody by Moriwaki, et al. [55]. In this study, Moriwaki, et al. came to the conclusion that in rats treated with infliximab levels of albuminuria and TNF- $\alpha$  urinary excretion were found to be decreased. An anti-inflammatory and immunosuppressive drug, mycophenolate mofetil effect was demonstrated recently by Utimura et al. in experimental diabetic nephropathy that mycophenolate mofetil was able to prevent the development of albuminuria and glomerular injury. Utimura et al. found that mycophenolate mofetil has immunosuppressive and

antiinflammatory properties as it result was not related to any effect on glomerular hemodynamics or improvement of metabolism [56].

## Conclusion

In the field of medicine Diabetic nephropathy remains as a major challenge. Prevention of DN development is still challenging. Till date, there is no treatment. Therefore, to intervene of DN novel therapeutic agents are still needed. Several proinflammatory cytokines are involved to activate the major signaling pathway huge number of evidence exists to prove these. Some proinflammatory cytokines like, IL-1, IL-6, and TNF- $\alpha$  are known to be involve in its mechanism. These cytokines play important role in development and progression of DN. Understanding this signaling pathway in detail will be beneficial in development of novel therapeutic approach. These therapeutic approaches may be helpful to interrupt DN development by intervening the inflammatory pathway.

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