



## **Global Conference on Medical and Health Sciences**

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

---

### **TYPE 2 DIABETES MELLITUS: FROM HYPERGLYCEMIA-INDUCED BIOCHEMICAL ALTERATIONS TO RENAL HISTOPATHOLOGY**

Azizbek Melikuziev

Giyosiddin Askaraliev

Azizbek Baratov

Umarkhon Mamatkhonov

Tashkent State Medical University, Tashkent, Uzbekistan

#### **Abstract**

**Background:** Type 2 diabetes mellitus is characterized by insulin resistance, progressive beta-cell dysfunction and chronic hyperglycemia. Persistent elevation of blood glucose initiates biochemical disturbances that affect vascular and renal cells long before advanced kidney failure becomes clinically evident. Among the best described mechanisms are increased advanced glycation end-product formation, activation of the polyol and protein kinase C pathways, increased hexosamine pathway flux, oxidative stress and inflammatory signaling. **Objective:** This narrative review summarizes the main hyperglycemia-induced biochemical alterations in type 2 diabetes and connects them with the characteristic histopathological changes of diabetic kidney disease. **Methods:** A narrative literature search was performed using PubMed and reference lists of major reviews. English-language articles on hyperglycemia, oxidative stress, advanced glycation, diabetic kidney disease, renal morphology, glomerular basement membrane changes, mesangial expansion, podocyte injury, nodular glomerulosclerosis, arteriolar hyalinosis and tubulointerstitial fibrosis were prioritized. Classic mechanistic and classification papers were retained when they remained relevant. **Results:** Chronic hyperglycemia increases mitochondrial and cytosolic oxidative stress and promotes several glucose-dependent pathways that



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

alter endothelial, mesangial, podocyte and tubular cell behavior. Hemodynamic changes, especially glomerular hyperfiltration and intraglomerular hypertension, act together with metabolic injury. The major renal structural lesions include glomerular basement membrane thickening, mesangial matrix expansion, Kimmelstiel-Wilson nodules, podocyte loss, arteriolar hyalinosis, tubular basement membrane thickening, tubular atrophy and interstitial fibrosis. The Renal Pathology Society classification organizes diabetic glomerular lesions from isolated basement membrane thickening to advanced glomerulosclerosis. Conclusion: Diabetic kidney disease is best understood as a whole-nephron process in which chronic hyperglycemia produces biochemical, hemodynamic and inflammatory disturbances that gradually become visible as characteristic renal histopathology. Understanding this sequence helps connect basic biochemistry with the microscopic findings encountered in pathology.

**Keywords:** type 2 diabetes mellitus; hyperglycemia; diabetic kidney disease; diabetic nephropathy; advanced glycation end products; oxidative stress; glomerulosclerosis; renal histopathology.

### 1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder in which insulin resistance and progressive pancreatic beta-cell dysfunction lead to persistent disturbances of glucose metabolism. Although hyperglycemia is the most obvious laboratory feature, the long-term clinical importance of diabetes is largely determined by its complications. The kidneys are among the organs most vulnerable to chronic metabolic and vascular injury. Diabetic kidney disease (DKD) is therefore one of the major microvascular complications of diabetes and an important cause of chronic kidney disease and kidney failure [1].



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

Diabetic renal injury does not develop through a single pathway. Hyperglycemia changes intracellular metabolism, promotes oxidative stress, alters protein structure through nonenzymatic glycation, activates signaling pathways such as protein kinase C (PKC), and influences inflammatory and profibrotic mediators. At the same time, changes in renal hemodynamics increase intraglomerular pressure and filtration. These metabolic and hemodynamic processes reinforce each other and affect nearly every major renal cell type, including glomerular endothelial cells, mesangial cells, podocytes, tubular epithelial cells and vascular smooth muscle cells [1-5].

Several biochemical pathways have been repeatedly linked to glucose toxicity. Brownlee proposed that hyperglycemia-driven mitochondrial superoxide production can activate or amplify multiple damaging pathways, including increased polyol pathway flux, advanced glycation end-product (AGE) formation, PKC activation and the hexosamine pathway [2,3]. More recent work has expanded this model by emphasizing inflammation, mitochondrial dysfunction, lipotoxicity, hypoxia, altered autophagy and cell-specific responses [4-9]. The older pathways remain useful, however, because they explain the basic connection between excess glucose and structural tissue injury.

The kidney provides an especially useful example of this connection because diabetic injury produces recognizable microscopic lesions. Early abnormalities may be subtle and sometimes require electron microscopy, such as glomerular basement membrane (GBM) thickening. With progression, light microscopy can show mesangial expansion, diffuse glomerulosclerosis, Kimmelstiel-Wilson nodules, arteriolar hyalinosis and eventually widespread glomerular sclerosis. The tubulointerstitial compartment may show tubular hypertrophy early and later tubular atrophy, basement membrane thickening, interstitial inflammation and fibrosis [6,8-12].



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

In T2DM, the relationship between clinical findings and histology is not always uniform. Some patients have classic diabetic glomerulopathy, while others have substantial vascular or tubulointerstitial injury with relatively mild glomerular lesions. Non-diabetic kidney diseases may also occur alone or together with diabetic lesions [11]. This heterogeneity is one reason why the terms diabetic kidney disease and diabetic nephropathy are not always used in exactly the same way. In this review, DKD refers broadly to kidney disease associated with diabetes, while diabetic nephropathy refers mainly to the characteristic structural renal lesions attributed to diabetes.

The purpose of this narrative review is to trace a clear sequence from chronic hyperglycemia to biochemical alterations and then to the major histopathological findings of diabetic renal injury. Particular attention is given to mechanisms that can be connected directly with recognizable changes in glomeruli, renal vessels, tubules and interstitium.

## 2. Methods

This article was prepared as a narrative review rather than a systematic review or meta-analysis. Literature was searched primarily through PubMed using combinations of the terms "type 2 diabetes mellitus," "hyperglycemia," "diabetic kidney disease," "diabetic nephropathy," "advanced glycation end products," "polyol pathway," "protein kinase C," "hexosamine pathway," "oxidative stress," "glomerular basement membrane," "mesangial expansion," "podocyte," "Kimmelstiel-Wilson," "arteriolar hyalinosis," "tubulointerstitial fibrosis" and "renal pathology."

Priority was given to peer-reviewed review articles, pathology-oriented papers, mechanistic studies and consensus or classification publications. Recent reviews were used to represent current understanding, while older highly cited papers



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

were retained for the classical biochemical mechanisms and the development of renal pathological classification. Because the aim was educational synthesis, no formal risk-of-bias tool, PRISMA flow diagram or quantitative pooling was performed.

The evidence was organized into three linked levels: first, biochemical effects of chronic hyperglycemia; second, renal cellular and hemodynamic responses; and third, visible histopathological lesions. This approach was chosen to keep the review focused on the transition from molecular mechanisms to renal morphology rather than providing a broad review of every clinical aspect of T2DM.

### 3. Results

#### 3.1. Hyperglycemia as the initiating metabolic stress

Chronic hyperglycemia exposes renal cells to an abnormally high glucose environment. This is particularly important in cells that cannot sufficiently reduce glucose entry when extracellular glucose rises. As intracellular glucose increases, more substrate enters glycolysis and related pathways. The resulting metabolic pressure alters redox balance, enzyme activity, gene expression and protein structure [2-5].

Hyperglycemia also has renal hemodynamic effects. In early diabetes, increased filtered glucose and sodium reabsorption in the proximal tubule reduces sodium chloride delivery to the macula densa. Tubuloglomerular feedback is therefore shifted toward afferent arteriolar dilation and increased glomerular filtration. The resulting hyperfiltration and intraglomerular pressure add mechanical stress to the glomerular capillary wall, podocytes and mesangial cells [1,14,15]. Metabolic and hemodynamic injury should therefore be viewed as parallel processes rather than competing explanations.



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

Prolonged exposure to hyperglycemia can continue to influence tissue even after glucose control improves. Persistent oxidative, epigenetic and extracellular matrix changes have been described as part of metabolic or hyperglycemic memory [4,5]. This helps explain why diabetic complications may continue to progress after years of previous poor control.

### 3.2. Oxidative stress and mitochondrial reactive oxygen species

Oxidative stress develops when production of reactive oxygen species (ROS) exceeds the capacity of antioxidant systems. Hyperglycemia can increase mitochondrial electron transport and promote superoxide generation. ROS can then damage lipids, proteins and nucleic acids and can also function as signaling molecules that activate inflammatory and profibrotic pathways [2-5].

In the diabetic kidney, oxidative stress affects glomerular endothelial cells, mesangial cells, podocytes and tubular epithelial cells. It promotes endothelial dysfunction, increases permeability, amplifies AGE signaling, contributes to PKC activation and can stimulate cytokines such as transforming growth factor-beta (TGF-beta). Oxidative stress therefore acts less like an isolated pathway and more like a central amplifier of multiple forms of diabetic tissue injury [4,5].

ROS are also linked to mitochondrial dysfunction and renal hypoxia. The kidney has high energy requirements, especially in the proximal tubule. Increased tubular reabsorption in diabetes raises oxygen consumption, while microvascular disease may reduce efficient oxygen delivery. This combination contributes to oxidative stress, inflammation and fibrosis in later DKD [1,7,15].

### 3.3. Advanced glycation end products and RAGE signaling

Advanced glycation end products form through nonenzymatic reactions between reducing sugars or reactive carbonyl compounds and proteins, lipids or nucleic



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

acids. Persistent hyperglycemia accelerates this process. Long-lived extracellular matrix proteins such as collagen are particularly vulnerable because glycated proteins may accumulate over time and resist normal degradation [2-4].

AGEs can alter tissue mechanically by cross-linking extracellular matrix proteins and can also act through the receptor for advanced glycation end products (RAGE). AGE-RAGE signaling activates oxidative stress, nuclear factor-kappa B and inflammatory pathways. In the kidney, these effects contribute to endothelial dysfunction, mesangial matrix production, podocyte injury and fibrosis [3,4,6].

From a histopathological perspective, chronic matrix accumulation is important because it contributes to GBM thickening, mesangial expansion and glomerulosclerosis. These lesions are not produced by AGEs alone, but AGE-related changes provide a biochemical explanation for why extracellular matrix becomes progressively excessive and abnormal in long-standing diabetes.

### 3.4. Polyol pathway activation

When intracellular glucose is high, more glucose can be reduced to sorbitol by aldose reductase. This reaction consumes NADPH, which is also needed to regenerate reduced glutathione. Increased polyol pathway activity may therefore weaken antioxidant capacity and contribute to oxidative stress [2-5]. Sorbitol can also create osmotic and metabolic disturbances in susceptible tissues.

The polyol pathway is classically discussed in diabetic complications because it links excess glucose directly with changes in redox state. Its contribution to renal injury is probably part of a larger network rather than an isolated dominant mechanism. In the kidney, the resulting oxidative imbalance can interact with PKC, AGE formation and inflammatory signaling.



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

---

### 3.5. Protein kinase C activation

Hyperglycemia increases intracellular diacylglycerol formation and can activate several PKC isoforms. PKC signaling alters vascular permeability, blood flow, endothelial function and expression of extracellular matrix proteins, cytokines and growth factors [2-4]. In glomeruli, these effects can increase vascular dysfunction and promote mesangial and basement membrane changes.

PKC activation also interacts with vascular endothelial growth factor, TGF-beta, nitric oxide pathways and NADPH oxidase. The result is a mixture of altered hemodynamics, oxidative stress and matrix production. Histologically, the important endpoint is progressive thickening and sclerosis rather than a unique lesion that can be identified as 'PKC-specific.'

### 3.6. Hexosamine pathway and altered gene regulation

Excess intracellular glucose can also enter the hexosamine biosynthetic pathway. The final products of this pathway participate in O-linked glycosylation of transcription factors and other proteins, thereby changing cellular signaling and gene expression [2-4]. Hyperglycemia-induced changes in the hexosamine pathway have been associated with increased expression of TGF-beta and other proteins involved in extracellular matrix production.

This pathway illustrates an important concept in diabetic complications: excess glucose does not simply provide more energy. It changes the biochemical modification of proteins and therefore changes how cells behave. Over years, small alterations in matrix synthesis, inflammatory signaling and cell survival can become visible as chronic structural lesions.



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

**Table 1.** Major hyperglycemia-related pathways and their relevance to renal injury.

| Biochemical alteration | Main effect                                                           | Possible renal consequence                                              |
|------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------|
| Oxidative stress       | Excess ROS, redox imbalance, mitochondrial dysfunction                | Endothelial, podocyte and tubular injury; inflammation and fibrosis     |
| AGE formation/RAGE     | Protein modification, matrix cross-linking, inflammatory signaling    | GBM thickening, mesangial matrix accumulation, vascular injury          |
| Polyol pathway         | Sorbitol production and NADPH consumption                             | Reduced antioxidant capacity and increased oxidative stress             |
| PKC activation         | Altered vascular signaling, permeability and growth-factor expression | Hemodynamic dysfunction, matrix deposition and sclerosis                |
| Hexosamine pathway     | O-GlcNAc-related changes in signaling and gene expression             | Profibrotic and matrix-producing cellular phenotype                     |
| TGF-beta signaling     | Cell hypertrophy and extracellular matrix synthesis                   | Mesangial expansion, glomerulosclerosis and tubulointerstitial fibrosis |

### 3.7. TGF-beta, extracellular matrix accumulation and fibrosis

TGF-beta is one of the best established profibrotic mediators in diabetic nephropathy. High glucose, AGEs, angiotensin II, oxidative stress and mechanical forces can increase TGF-beta activity. TGF-beta promotes renal cell hypertrophy and stimulates synthesis of extracellular matrix components including collagen and fibronectin [16,17].

In mesangial cells, increased TGF-beta activity contributes to matrix expansion. In tubular and interstitial compartments, it promotes a profibrotic environment involving fibroblasts, myofibroblasts and altered epithelial signaling. This provides a direct molecular bridge between chronic hyperglycemia and the excess



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

extracellular matrix that is later seen histologically as glomerulosclerosis and interstitial fibrosis.

Fibrosis represents a final common pathway of many chronic renal injuries. In diabetes, it is produced by the combined effects of metabolic stress, hemodynamic injury, inflammation, hypoxia and growth-factor signaling rather than by TGF-beta alone [7-9,17].

### 3.8. Glomerular basement membrane thickening

One of the earliest characteristic structural abnormalities of diabetic nephropathy is diffuse thickening of the GBM. In early disease, light microscopy may appear nearly normal, and electron microscopy is more sensitive. GBM thickening reflects altered production and turnover of basement membrane components and develops in the setting of chronic hyperglycemia and abnormal matrix metabolism [10,13].

The thickened GBM does not function as a stronger filter. Instead, changes in composition and organization occur together with endothelial glycocalyx injury and podocyte abnormalities. These changes reduce the selectivity of the glomerular filtration barrier and contribute to albumin leakage [13].

In the Renal Pathology Society classification, class I diabetic nephropathy is defined by isolated GBM thickening with only mild or nonspecific light microscopic changes that do not meet criteria for more advanced classes [10].

### 3.9. Mesangial expansion and diffuse glomerulosclerosis

Mesangial expansion is a central morphological feature of established diabetic glomerulopathy. It results mainly from increased mesangial matrix, with a smaller contribution from changes in mesangial cell number. Histologically, the mesangial regions become broader and progressively occupy more of the



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

glomerular tuft. With progression, capillary lumina may become compressed and filtration surface area is lost [10-13].

Biochemically, mesangial matrix expansion can be linked to high-glucose signaling, AGE accumulation, oxidative stress, PKC activity, angiotensin II and especially TGF-beta-mediated matrix synthesis [16,17]. Mechanical stress from intraglomerular hypertension may add another stimulus. The relationship is therefore a good example of metabolic and hemodynamic mechanisms converging on one structural lesion.

The Renal Pathology Society separates mesangial expansion into class IIa and IIb according to severity, provided that nodular sclerosis and advanced global glomerulosclerosis are absent [10]. Mesangial expansion also has functional importance. Structural studies in patients with type 2 diabetes have shown relationships between glomerular pathology, proteinuria and renal function [12].

### 3.10. Kimmelstiel-Wilson nodules

Nodular glomerulosclerosis is one of the classic lesions associated with diabetic nephropathy. Kimmelstiel-Wilson nodules are round or oval accumulations of mesangial matrix that expand part of the glomerular tuft. They are usually accompanied by diffuse mesangial expansion and basement membrane abnormalities.

In the Renal Pathology Society system, the presence of at least one convincing Kimmelstiel-Wilson lesion, in the absence of criteria for advanced class IV disease, defines class III diabetic nephropathy [10]. Nodular sclerosis is strongly suggestive of diabetes in the correct clinical setting, but it is not completely specific. Similar nodular patterns can occur in conditions such as monoclonal immunoglobulin deposition disease, amyloidosis and smoking-related nodular



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

glomerulosclerosis. Clinical information, immunofluorescence and electron microscopy may therefore be required when the diagnosis is uncertain.

The nodule itself represents a late consequence of progressive extracellular matrix accumulation. Hyperglycemia-related biochemical pathways are thus connected to the lesion indirectly through years of altered matrix production, degradation and vascular stress.

### 3.11. Podocyte injury and loss

Podocytes are highly specialized epithelial cells that cover the outer surface of glomerular capillaries and are essential for maintaining the filtration barrier. Diabetes can cause podocyte hypertrophy, foot-process effacement, altered slit-diaphragm proteins, detachment and apoptosis [13,18]. Because mature podocytes have limited proliferative capacity, podocyte loss is difficult to replace. Hyperglycemia, AGEs, ROS, mechanical stretch, angiotensin II and TGF-beta have all been implicated in podocyte injury. As podocytes detach, portions of the GBM may become insufficiently covered and more permeable to albumin. Progressive podocyte depletion also favors segmental and global glomerulosclerosis [18].

These changes help explain why diabetic nephropathy cannot be understood only as a mesangial disease. The filtration barrier is a functional unit involving endothelium, GBM and podocytes, and diabetes alters all three components [13].

### 3.12. Arteriolar hyalinosis and vascular lesions

Diabetes produces characteristic vascular changes within the kidney. Arteriolar hyalinosis results from accumulation of plasma proteins and extracellular material in arteriolar walls, producing a homogeneous eosinophilic appearance on routine staining. Both afferent and efferent arterioles may be involved, and



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

prominent efferent arteriolar hyalinosis is particularly suggestive of diabetes in the appropriate clinical context.

Arteriosclerosis with intimal thickening may coexist, especially in patients with hypertension and aging. Vascular narrowing contributes to chronic ischemic injury and can worsen tubulointerstitial fibrosis. In the Renal Pathology Society system, arteriolar hyalinosis and arteriosclerosis are scored separately from the main glomerular class [10].

These vascular lesions again reflect the combined effects of glycation, endothelial dysfunction, hypertension and chronic metabolic stress. They also help explain why renal injury in type 2 diabetes may be structurally heterogeneous [11].

### 3.13. Tubular and interstitial lesions

The tubulointerstitial compartment is increasingly recognized as a major determinant of progression in DKD. Early diabetes can produce tubular hypertrophy and increased proximal tubular workload. Later, persistent high glucose exposure, filtered proteins, AGEs, oxidative stress, hypoxia and inflammatory mediators contribute to tubular injury and interstitial inflammation [7,9,15,19].

Histologically, advanced disease may show tubular basement membrane thickening, tubular atrophy, interstitial fibrosis and loss of peritubular capillaries. Interstitial fibrosis and tubular atrophy correlate strongly with loss of renal function in many chronic kidney diseases, including diabetic nephropathy. This is one reason modern descriptions of DKD no longer focus only on the glomerulus [7-9,19].

Proteinuria can further damage proximal tubular cells by increasing the amount of filtered protein that must be handled. Tubular cells respond by producing inflammatory and profibrotic signals, which can recruit immune cells and activate



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

interstitial fibroblasts. A cycle then develops in which glomerular injury increases tubular stress and tubulointerstitial damage further reduces nephron function.

### 3.14. Renal Pathology Society classification

The 2010 Renal Pathology Society classification provides a practical framework for grading the glomerular lesions of diabetic nephropathy while separately scoring tubulointerstitial and vascular changes [10]. It applies to diabetic nephropathy in both type 1 and type 2 diabetes and remains widely used in renal pathology.

**Table 2.** Simplified Renal Pathology Society classification of diabetic nephropathy [10].

| Class | Main glomerular finding                                                                                                 |
|-------|-------------------------------------------------------------------------------------------------------------------------|
| I     | Isolated GBM thickening confirmed by electron microscopy, with only mild or nonspecific light microscopic changes.      |
| IIa   | Mild mesangial expansion without Kimmelstiel-Wilson nodules or advanced global glomerulosclerosis.                      |
| IIb   | Severe mesangial expansion without Kimmelstiel-Wilson nodules or advanced global glomerulosclerosis.                    |
| III   | At least one convincing Kimmelstiel-Wilson nodule, without class IV changes.                                            |
| IV    | Advanced diabetic glomerulosclerosis with more than 50% global glomerulosclerosis attributable to diabetic nephropathy. |

Interstitial fibrosis and tubular atrophy, interstitial inflammation, arteriolar hyalinosis and arteriosclerosis are assessed separately. This is useful because patients with the same glomerular class may have different degrees of vascular and tubulointerstitial injury.



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

---

### 4. Discussion

The main purpose of this review was to connect chronic hyperglycemia with the structural renal lesions seen in diabetic kidney disease. The connection is not a straight line in which one biochemical pathway produces one microscopic lesion. Instead, hyperglycemia initiates several overlapping pathways that produce oxidative stress, endothelial dysfunction, abnormal matrix metabolism, inflammation and altered cell survival. Hemodynamic stress occurs at the same time. Over years, these processes are expressed histologically as changes in the glomerular filtration barrier, mesangium, renal vasculature and tubulointerstitium [1,4,6-9].

The classical hyperglycemia pathways remain educationally useful. Increased mitochondrial ROS, AGE formation, polyol pathway flux, PKC activation and the hexosamine pathway explain how an extracellular increase in glucose can alter intracellular signaling and tissue proteins [2-5]. However, current understanding goes beyond this classical scheme. Mitochondrial dysfunction, hypoxia, lipotoxicity, inflammation, autophagy, immune-cell signaling and cell-specific metabolic changes are also involved in DKD [1,6-9]. Therefore, the older pathways should be regarded as a foundation rather than a complete description. The glomerular lesions show a recognizable progression. Early basement membrane thickening may precede obvious light microscopic abnormalities. Mesangial matrix then expands, and some patients develop nodular glomerulosclerosis. Podocyte injury reduces the ability of the filtration barrier to retain albumin. With severe progression, increasing numbers of glomeruli become globally sclerosed and nephron number falls [10,13,18].

T2DM adds an important layer of complexity because renal lesions are not uniform. Biopsy studies show that some patients with T2DM and renal dysfunction have classic glomerulopathy, while others have less severe diabetic



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

glomerular injury, prominent arteriosclerosis or tubulointerstitial disease. Non-diabetic kidney diseases may also be present [11]. This is clinically important because albuminuria or a fall in estimated glomerular filtration rate does not automatically prove that every renal lesion is caused by diabetes.

Kidney biopsy is not routinely required for all patients with diabetes and CKD. In many cases, the diagnosis is clinical. Biopsy becomes more important when the presentation is atypical, for example rapid loss of renal function, active urinary sediment, sudden nephrotic-range proteinuria, a short duration of diabetes or features suggesting another glomerular disease. In such cases, histology can distinguish classic diabetic nephropathy from non-diabetic or mixed renal disease.

Treatment also supports the idea that DKD is driven by more than glucose alone. Glycemic control remains important, but current management also targets blood pressure, the renin-angiotensin system and renal hemodynamics. SGLT2 inhibitors reduce proximal tubular sodium-glucose reabsorption and alter tubuloglomerular feedback, lowering intraglomerular pressure while also producing additional metabolic and protective effects [1,14,20,21]. Current diabetes-CKD guidance therefore combines glucose-lowering therapy with agents shown to reduce renal and cardiovascular risk [20].

From a pathology perspective, treatment cannot be expected to reverse every established structural lesion. Advanced glomerulosclerosis and interstitial fibrosis represent loss and replacement of functioning renal tissue. This makes prevention of progression particularly important. Earlier biochemical and functional abnormalities may be more modifiable than late scar formation.

The strongest educational value of this topic is the way it joins biochemistry with morphology. AGE formation, ROS, PKC activation and TGF-beta signaling can feel abstract when studied separately. Renal histology shows their long-term



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

consequences. A thickened GBM, expanded mesangium or fibrotic interstitium represents years of altered cell signaling, matrix production, vascular stress and incomplete repair.

### 4.1. Limitations

This review is narrative and was designed as an educational synthesis. It does not provide a systematic search strategy, formal quality assessment or meta-analysis. The included evidence spans different study types, including experimental studies, human biopsy studies, reviews and consensus papers.

Another limitation is that biochemical pathways are often studied in experimental systems where individual mechanisms can be isolated more easily than in human disease. Human DKD develops in the presence of additional factors such as hypertension, obesity, dyslipidemia, aging, medication use and genetic susceptibility. For this reason, direct one-to-one statements between a molecular pathway and a histological lesion should be avoided.

Finally, diabetic kidney disease in T2DM is heterogeneous. The Renal Pathology Society classification is useful for diabetic glomerular lesions but does not remove the need to assess vascular, interstitial and potentially non-diabetic abnormalities in a complete renal biopsy.

### 5. Conclusion

Type 2 diabetes mellitus produces chronic renal injury through the interaction of persistent hyperglycemia, altered cellular metabolism, oxidative stress, inflammatory and profibrotic signaling, and abnormal renal hemodynamics. Hyperglycemia increases AGE formation, polyol pathway flux, PKC activity and hexosamine pathway signaling while promoting ROS production and TGF-beta-mediated matrix accumulation. These biochemical changes gradually become



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

visible as characteristic renal structural abnormalities. The major lesions include GBM thickening, mesangial expansion, Kimmelstiel-Wilson nodules, podocyte injury, arteriolar hyalinosis, tubular atrophy and interstitial fibrosis. The Renal Pathology Society classification provides a useful framework for organizing glomerular severity, but DKD should be considered a whole-nephron disease involving glomerular, vascular and tubulointerstitial compartments. Connecting hyperglycemia-induced biochemical alterations with renal histopathology provides a practical way to understand diabetic complications and demonstrates how long-term metabolic disturbance is translated into permanent tissue injury.

## References

1. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. *Nat Rev Nephrol.* 2021;17(5):319-334. doi:10.1038/s41581-021-00393-8.
2. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001;414(6865):813-820. doi:10.1038/414813a.
3. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes.* 2005;54(6):1615-1625. doi:10.2337/diabetes.54.6.1615.
4. Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev.* 2013;93(1):137-188. doi:10.1152/physrev.00045.2011.
5. Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circ Res.* 2010;107(9):1058-1070. doi:10.1161/CIRCRESAHA.110.223545.
6. Jha R, Lopez-Trevino S, Kankanamalage HR, Jha JC. Diabetes and renal complications: an overview on pathophysiology, biomarkers and therapeutic interventions. *Biomedicines.* 2024;12(5):1098. doi:10.3390/biomedicines12051098.



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

7. Hung PH, Hsu YC, Chen TH, Lin CL. Recent advances in diabetic kidney diseases: from kidney injury to kidney fibrosis. *Int J Mol Sci.* 2021;22(21):11857. doi:10.3390/ijms222111857.
8. Thomas MC. Targeting the pathobiology of diabetic kidney disease. *Adv Chronic Kidney Dis.* 2021;28(4):282-289. doi:10.1053/j.ackd.2021.07.001.
9. Ricciardi CA, Gnudi L. Kidney disease in diabetes: from mechanisms to clinical presentation and treatment strategies. *Metabolism.* 2021;124:154890. doi:10.1016/j.metabol.2021.154890.
10. Tervaert TWC, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, et al. Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol.* 2010;21(4):556-563. doi:10.1681/ASN.2010010010.
11. Di Vincenzo A, Bettini S, Russo L, Mazzocut S, Mauer M, Fioretto P. Renal structure in type 2 diabetes: facts and misconceptions. *J Nephrol.* 2020;33(5):901-907. doi:10.1007/s40620-020-00797-y.
12. White KE, Bilous RW. Type 2 diabetic patients with nephropathy show structural-functional relationships that are similar to type 1 disease. *J Am Soc Nephrol.* 2000;11(9):1667-1673. doi:10.1681/ASN.V1191667.
13. Demirci H. Glomerular alteration in diabetic kidney disease: from morphology to metabolism. *Kidney Res Clin Pract.* 2025. doi:10.23876/j.krcp.24.294.
14. Vallon V, Thomson SC. The tubular hypothesis of nephron filtration and diabetic kidney disease. *Nat Rev Nephrol.* 2020;16(6):317-336. doi:10.1038/s41581-020-0256-y.
15. Vallon V. The proximal tubule in the pathophysiology of the diabetic kidney. *Am J Physiol Regul Integr Comp Physiol.* 2011;300(5):R1009-R1022. doi:10.1152/ajpregu.00809.2010.



## Global Conference on Medical and Health Sciences

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

16. Chang AS, Hathaway CK, Smithies O, Kakoki M. Transforming growth factor-beta1 and diabetic nephropathy. *Am J Physiol Renal Physiol*. 2016;310(8):F689-F696. doi:10.1152/ajprenal.00502.2015.
17. Wang L, Wang HL, Liu TT, Lan HY. TGF-Beta as a master regulator of diabetic nephropathy. *Int J Mol Sci*. 2021;22(15):7881. doi:10.3390/ijms22157881.
18. Zhang L, Wen Z, Han L, Zheng Y, Wei Y, Wang X, et al. Research progress on the pathological mechanisms of podocytes in diabetic nephropathy. *J Diabetes Res*. 2020;2020:7504798. doi:10.1155/2020/7504798.
19. Gilbert RE, Cooper ME. The tubulointerstitium in progressive diabetic kidney disease: more than an aftermath of glomerular injury? *Kidney Int*. 1999;56(5):1627-1637. doi:10.1046/j.1523-1755.1999.00721.x.
20. de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association and Kidney Disease: Improving Global Outcomes. *Kidney Int*. 2022;102(5):974-989. doi:10.1016/j.kint.2022.08.012.
21. Sen T, Heerspink HJL. A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. *Cell Metab*. 2021;33(4):732-739. doi:10.1016/j.cmet.2021.02.016.
22. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol*. 2017;12(12):2032-2045. doi:10.2215/CJN.11491116.
23. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA consensus conference. *Am J Kidney Dis*. 2014;64(4):510-533. doi:10.1053/j.ajkd.2014.08.001.



## **Global Conference on Medical and Health Sciences**

Hosted Online from Madrid, Spain

Date: 14<sup>th</sup> September, 2026

Website: <https://econferencia.com>

---

24. Sharma K, Ziyadeh FN. Hyperglycemia and diabetic kidney disease. The case for transforming growth factor-beta as a key mediator. Diabetes. 1995;44(10):1139-1146. doi:10.2337/diab.44.10.1139.

### **Declarations**

Conflict of interest: The authors declare no conflict of interest.

Funding: No external funding was received for preparation of this review.

Author contributions: To be completed after the authors agree on final roles.

Acknowledgements: None at draft stage.