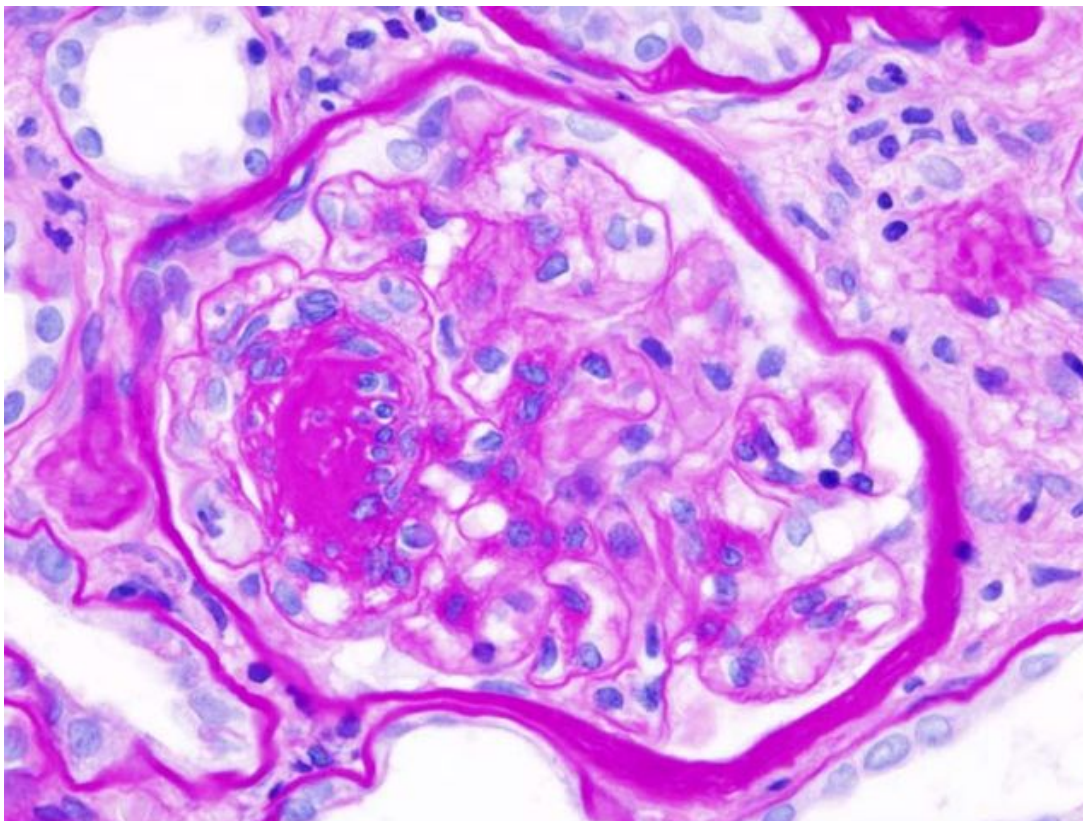


Diabetic Glomerulopathy — Pathogenesis and Management

[See online here](#)

Diabetic glomerulopathy is the leading cause of chronic renal failure in adults. Long-standing type 1 or type 2 diabetes mellitus is associated with this microvascular complication, along with peripheral neuropathy and retinopathy. The pathology of diabetic glomerulopathy is distinguishable based on certain features, including the presence of pathognomonic Kimmelstiel-Wilson nodules, hence the term Kimmelstiel-Wilson disease. A diagnosis of diabetic glomerulopathy does not require a renal biopsy - rather, it is established based on the presence of significant proteinuria and a history of diabetes for >10 years or diabetic retinopathy. Students should be aware about this important complication of diabetes, including its pathology, pathophysiology, clinical course and management.



Definition and Epidemiology of Diabetic Glomerulopathy

Diabetic glomerulopathy refers to a **glomerular disease** that is caused by **diabetes**. It is synonymous with the commonly used term **diabetic nephropathy**.

It is the **most common cause of chronic renal failure** in adults. It accounts for **45% of renal transplants**. The increasing problem of diabetic glomerulopathy reflects the **increasing prevalence of type 2 diabetes, obesity, and metabolic syndrome**.

The risk of diabetic glomerulopathy differs for type 1 and type 2 diabetes. The **risk is higher in type 1 diabetes**; with about 30 – 40% of type 1 diabetics developing nephropathy after 20 years; whereas, the risk in type 2 diabetes is 15 – 20% after 20 years. The higher risk of end-stage renal disease in type 1 diabetes may be because these patients have a lower incidence of comorbidities and mortalities before renal complications occur.

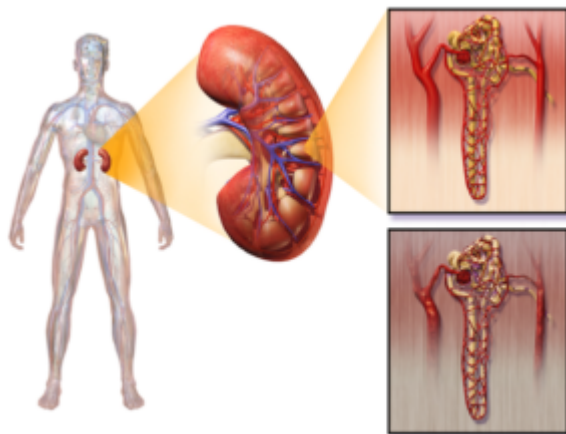


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Given that type 2 diabetes is a lot more common (90% prevalence) than type 1 diabetes (10% prevalence), those with type 2 diabetes account for the vast majority of patients with diabetic glomerulopathy.

As a result of diabetic glomerulopathy, up to 40% of type 1 and type 2 diabetics develop **end-stage renal failure**. Renal failure is the second most common cause of mortality in patients with diabetes, following cardiovascular disease.

Males have a higher risk of developing diabetic glomerulopathy. There are also **ethnic differences**, with an increased risk among patients of African American, Native American, Maori or Polynesian descent.

Etiology of Diabetic Glomerulopathy

There are a number of risk factors associated with the development of diabetic glomerulopathy. **Persistent hyperglycemia**, or glucotoxicity, plays a primary role. It is well known that controlling glucose levels is important in preventing or delaying the onset of long-term complications of diabetes, such as diabetic glomerulopathy.

Aside from hyperglycemia, there are other factors at play as well. These include **hypertension, hyperlipidemia, smoking, physical inactivity** and **high dietary intake of fat and protein**.

Genetic factors also play an important role. A **family history** of diabetic glomerulopathy is associated with a heightened risk. **Gene polymorphisms** involving the renin-angiotensin-aldosterone axis have also been implicated.

Pathology and Pathophysiology of Diabetic Glomerulopathy

Diabetic glomerulopathy at a cellular level

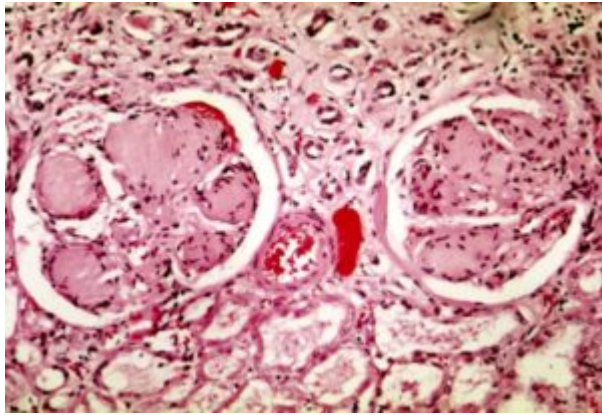


Image: "Nodular Glomerulosclerosis." License: Public Domain

The key features of diabetic glomerulopathy include **thickening of the capillary basement membrane**, **diffuse mesangial sclerosis**, as well as **nodular glomerular sclerosis**. The histopathologic appearance of diabetic glomerulopathy is predominantly similar in type 1 and 2 diabetes.

Glomerular capillary basement membrane thickening is almost always present in diabetic glomerulopathy. It is a feature of **diabetic microangiopathy**, which is related to the process of diffuse basement membrane thickening that occurs in capillaries in vascular structures (e.g. the retina, skin and skeletal muscle), as well as non-vascular structures (e.g. renal tubules and peripheral nerves). These changes appear early on in the glomerulus, within 1 to 2 years of the onset of diabetes.

Despite the thickened membranes, **capillaries have increased leakiness to plasma proteins**. Thickening of the basement membrane is accompanied by **mesangial widening**. Renal tubular basement membrane thickening also occurs.

The **mesangial matrix undergoes expansion** with the accumulation of extracellular matrix. **Increased mesangial matrix and sclerosis** also contribute to thickening of the glomerular basement membrane. It should be noted that the extent of mesangial expansion is associated with the degree of renal impairment and proteinuria.

Nodular glomerulosclerosis is pathognomonic of diabetic glomerulopathy and is also known as **Kimmelstiel-Wilson disease**. Glomerulosclerosis occurs in about 15 to 30% of patients. The nodules, called Kimmelstiel-Wilson nodules, are composed of eosinophilic, Periodic acid-Schiff (PAS) positive acellular matrix.

They are **ovoid or spherical** in shape and are located in the **periphery of the glomeruli, within the mesangium**. Kimmelstiel-Wilson nodules do not usually affect all lobules within a single glomerulus; however, diffuse mesangial sclerosis is present throughout. With time, **the nodules expand**, sometimes to a point where they **compress surrounding capillaries and may destroy the glomerulus** altogether.

Along with Kimmelstiel-Wilson nodules, **hyalinosis** is also present, affecting both afferent and efferent arterioles of the glomerulus. In capillary loops, they are called **fibrin caps**,

and, in Bowman capsules, they are referred to as **capsular drops**.

The pathological changes and damage to the glomeruli and arterioles in diabetic glomerulopathy lead to **ischemia**. Subsequently, **interstitial fibrosis and tubular atrophy** develop, and these changes result in **contraction of the kidney**. Clinically, **glomerulosclerosis often corresponds with the presence of renal failure**.

One of the key causes of the pathological changes in diabetic glomerulopathy is **persistent hyperglycemia**. Hyperglycemia results in **nephropathy** through various mechanisms, including:

- Advanced glycation end products (AGEs)
- Activation of protein kinase C (PKC)
- Oxidative stress
- Fructose-6-phosphate

Advanced glycation end products (AGEs)

Glucose attaches to the amino groups of intracellular and extracellular proteins by non-enzymatic reactions, forming AGEs. AGEs bind to cells, such as endothelial cells and vascular smooth muscle, via the **RAGE receptor**.

This stimulates the production of cytokines and growth factors, like Transforming Growth Factor β (TGF β), leading to basement membrane thickening. Other effects include the production of reactive oxygen species in endothelium and increased synthesis of extracellular matrix.

AGEs also **crosslink with extracellular matrix proteins**, leading to increased protein deposition. AGEs in the basement membrane trap nonglycated proteins such as albumin, which contributes to membrane thickening.

Activation of protein kinase C (PKC)

Hyperglycemia within cells leads to **synthesis of diacylglycerol (DAG)**, resulting in **excessive activation of PKC**. This causes **stimulation of profibrogenic growth factors** such as TGF β , contributing to **microangiopathy**.

Oxidative stress

Increased intracellular glucose in cells is metabolized by **aldose reductase** into sorbitol and then fructose. The consumption of antioxidants, via the aldose reductase pathway, makes cells more susceptible to oxidative stress.

Fructose-6-phosphate

Hyperglycemia causes increased levels of fructose-6-phosphate in cells through the **hexosamine pathway**. Fructose-6-phosphate acts as a substrate for **protein glycosylation**, leading to excess production of **proteoglycans**.

Other factors also play a role in diabetic glomerulopathy. **Intraglomerular hypertension** is a key process, possibly related to the effect of hyperglycemia on the **actin cytoskeleton** of vascular smooth muscle and mesangial cells.

There are also changes in **circulating factors**, including insulin-like growth factor (IGF), angiotensin and atrial natriuretic peptide. Persistent intraglomerular hypertension leads

to an **increase in matrix production and glomerulosclerosis**. It also causes changes to the glomerular basement membrane that disrupt the filtration barrier and contributes to **proteinuria**.

Symptoms of Diabetic Glomerulopathy

Diabetic glomerulopathy can present with the following signs and symptoms:

- Microalbuminuria
- Macroalbuminuria or proteinuria
- **Hypertension**
- Nephrotic syndrome

Symptoms are usually not apparent in the early stages of diabetic glomerulopathy. Rather, patients present with the detection of signs.

Notably, the earliest sign of diabetic nephropathy is **hyperfiltration**, indicated by an **increased GFR**.

Another early sign is the presence of **albumin in the urine** or **microalbuminuria**, at a quantity between 30 – 300mg/24h (hence “micro,” as these levels are not detected by dipstick urinalysis). Generally, patients develop microalbuminuria about 5 to 10 years following the onset of diabetes.

Following the onset of microalbuminuria, patients progressively excrete higher quantities of albumin in the urine to levels greater than 300mg/24h (**macroalbuminuria**) after another 5 to 10 years. This is usually accompanied by the presence of **hypertension**.

Nephrotic syndrome is a late manifestation of diabetic glomerulopathy, with patients presenting with proteinuria, hyperlipidemia, peripheral edema, and hypertension.

Many patients present with symptoms when they develop advanced disease. Such symptoms include **fatigue**, **anorexia**, **edema** and other features that occur with the onset of uremia (end-stage renal failure).

Diagnosis of Diabetic Glomerulopathy

Diabetic glomerulopathy is diagnosed based on a combination of history, clinical findings, and lab tests. While a renal biopsy enables a conclusive diagnosis, it is not typically performed as other tests are often more than adequate in formulating a diagnosis of diabetic glomerulopathy.

Lab tests

Patients have a **diagnosis of diabetes**, with **hyperglycemia** established based on **fasting blood glucose levels**.

Urine testing for microalbuminuria forms the most important initial evaluation for diabetic glomerulopathy. This can be detected with a **radiosensitive assay**. Higher levels are detectable with **urine dipstick testing**, and quantified with a **24-hour urine test or a protein-to-creatinine ratio** on a urine spot test. Proteinuria levels can vary greatly in patients, from 500mg to 25g/24h. Significant proteinuria usually results in **nephrotic syndrome** in patients (nephrotic range proteinuria is >3g/24h).

Current recommendations are for **screening patients for microalbuminuria early on**.

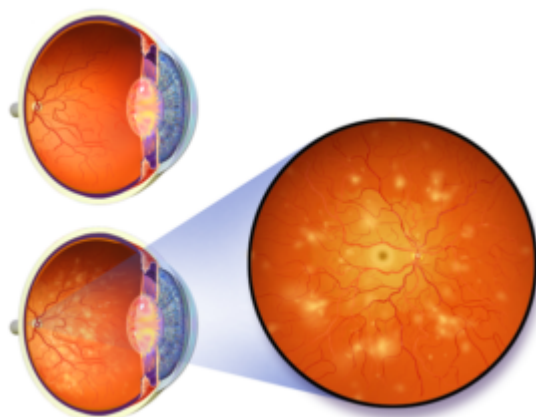
For type 1 diabetics, screening should commence 5 years after diagnosis and then on a **yearly basis**. For type 2 diabetics, screening usually occurs at the point of diagnosis and thereafter on a yearly basis.

The reason for this disparity is that the onset of type 2 diabetes is uncertain and often occurs later in many cases. In fact, cases of advanced diabetic nephropathy are not unheard of in patients newly diagnosed with type 2 diabetes.

In addition, **kidney function tests** are important in detecting the presence of renal failure. Patients with advanced disease have **elevated creatinine and urea levels**. **GFR calculation** is important – one of the first signs in diabetic glomerulopathy is **hyperfiltration**. However, with the onset of microalbuminuria and, as the disease progresses, patients experience **a decline in GFR**.

Imaging

In cases of advanced diabetic glomerulopathy, patients have **enlarged kidneys**. This is in contrast to other glomerular diseases where the kidneys are shrunken. A **renal ultrasound** is helpful in detecting enlarged kidneys in diabetic glomerulopathy, as well as ruling out other causes of renal pathology such as obstruction, [cysts](#) or a mass.



[Image](#): "Diabetic Retinopathy." by Blausen.com staff. "Blausen Gallery 2014". Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010. ISSN 20018762. - Own Work. License: [CC BY 3.0](#)

Ophthalmological testing

While not a diagnostic test for diabetic glomerulopathy, **testing for diabetic retinopathy** is important as its presence or absence can potentially support or preclude its diagnosis. Indeed, some diagnostic criteria for diabetic glomerulopathy requires the demonstration of proteinuria alongside a history of diabetes for >10 years or the presence of diabetic retinopathy.

New Biomarkers of Diabetic Glomerulopathy

Biomarkers of diabetic glomerulopathy can be classified into urinary markers, serum/plasma markers, and other novel biomarkers.

Urinary Biomarkers:

- Urinary albumin excretion (UAE) is a measurement of albumin excreted in the urine. 24 h or overnight urine collections are used to measure UAE.
- Urinary non-albumin protein-to-creatinine ratio. Urinary non-albumin proteins are excreted when there is a renal tubular injury. They include alpha-1-microglobulin, beta-2-microglobulin, IgG, cystatin C, transferrin, nephrin, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinase-1. Cystatin C excretion is highly correlated with GFR and can be a useful marker in patients with diabetic nephropathy.

Plasma/Serum Biomarkers:

- Cystatin C is superior to creatinine measurement in the assessment of kidney function because it is completely not bound to a carrier protein and is clearly correlated with GFR.

Other Novel Biomarkers:

- Metabolomics, metabonomics, genomics, and specific micro-RNAs are also emerging as novel biomarkers of diabetic nephropathy.

Differential Diagnosis of Diabetic Glomerulopathy

- **Glomerulonephritis:** e.g., lupus nephritis; signs and symptoms of other systemic disorders may be present.
- **Nephrotic syndrome:** has a range of other causes, apart from diabetic glomerulopathy, including primary diseases such as minimal change nephropathy, membranous nephropathy, and [membranoproliferative glomerulosclerosis](#), as well as other secondary causes such as amyloidosis and viral infections e.g. HCV.
- **Renal artery stenosis:** may present with refractory hypertension or renal failure. Patients have an abdominal bruit and the diagnosis is clear on imaging.
- **Multiple myeloma:** proteinuria and renal failure may be featured, but other key features include bone pain and [anemia](#).
- **Renovascular hypertension**

Therapy for Diabetic Glomerulopathy

The earlier the therapy, the better the outcomes. **Aggressive therapy** is important when patients develop microalbuminuria, one of the first signs of diabetic glomerulopathy.

Tight glycemic control is a central aspect of treatment. In type 1 diabetes, **regular insulin** is paramount. In type 2 diabetes, **glucose-lowering medication** and insulin are both options.

Glucose-lowering agents include biguanides (metformin), sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-IV inhibitors, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptide-1 agonists. When medications are inadequate in achieving glycemic control, insulin can be used, often in conjunction with metformin.

Blood pressure should also be closely managed with **anti-hypertensive medication**. In particular, drugs inhibiting the renin-angiotensin-aldosterone system are first-line - **ACE inhibitors** (Angiotensin Converting Enzyme inhibitors) or **ARBs** (Aldosterone Receptor

Blockers). The addition of a mineralocorticoid receptor blocker to an ACE inhibitor or an ARB was shown to have benefit in treating proteinuria in patients with diabetic nephropathy.

Bearing in mind that angiotensin causes an increased resistance of efferent arterioles and therefore increased glomerular capillary pressure; these drugs have the effect of dilating the efferent arteriole, thereby decreasing glomerular pressure.

They also inhibit **angiotensin II-mediated sclerosis**. If additional blood pressure control is needed, other classes of drugs can be added, such as a [calcium channel blocker](#), or a [thiazide diuretic](#). Most patients will require three or more antihypertensive drugs to control their blood pressure.

Blood pressure management decreases proteinuria and delays the progression of nephropathy, even in patients who are normotensive. The blood pressure target for patients with overt proteinuria is less than 130/80 mmHg. Blood pressure control in patients with diabetic glomerulopathy reduces not only the risk of renal complications but also cardiovascular events.

Also, given that microalbuminuria is an indicator of greatly increased cardiovascular risk, patients should be screened for and receive **aggressive therapy for cardiovascular risk factors**. The addition of a statin is beneficial to the patient even when the patient has normal low-density lipoprotein levels and can help in preventing long-term complications of diabetes mellitus.

Patients who develop end stage renal failure will require dialysis or renal transplantation.

Progression and Prognosis of Diabetic Glomerulopathy

The natural history of diabetic glomerulopathy is the eventual progression to **end-stage renal disease**, but not all patients will experience this outcome. Over 75% of type 1 diabetics with overt **nephropathy** (or **macroalbuminuria**) will progress to end-stage renal failure.

However, only about 20% of type 2 diabetics with overt nephropathy will progress to end-stage renal failure. It is worth mentioning that many patients with type 2 diabetes and microalbuminuria die from **cardiovascular events** before developing significant proteinuria or renal failure.

With the onset of microalbuminuria, one of the earliest features of diabetic glomerulopathy, it takes about 10 to 20 years until progression to end-stage renal disease.

Patients who develop **renal failure** and are on [dialysis](#) have lower survival rates compared to patients on dialysis for other conditions. However, there is improved survival in type 1 diabetic patients who undergo renal [transplantation](#) from a living relative.

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