Diabetic nephropathy and retinopathy
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Diabetic nephropathy (DN) and diabetic retinopathy (DR) are arguably the two most dreaded complications of diabetes. Together they contribute to serious morbidity and mortality. As they progress to end-stage renal disease (ESRD) and blindness, they impose enormous medical, economic, and social costs on both the patient and the health care system. Because nephropathy and retinopathy are frequently linked in patients, this article reviews their common and individual aspects of pathophysiology, clinical features, and management.

Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, arterial blood pressure elevation, a relentless decline in glomerular filtration rate (GFR), and a high risk of cardiovascular morbidity and mortality. This major life-threatening complication develops in approximately 20% to 40% of type 1 and less than 20% of type 2 diabetic patients [1]. DN is the leading known cause of ESRD in the United States, accounting for an estimated 28,000 new cases of ESRD per year [1].

Retinopathy is a serious microvascular complication of diabetes mellitus and the leading cause of blindness in adults less than 65 years of age. It is estimated that about 5.5 million adult patients with diabetes have DR. About 50,000 new cases of blindness occur per year, out of which 50% are caused by diabetes and most caused by DR [2].

Both ESRD and blindness are preventable through early detection and treatment. This article discusses the pathophysiology of these disorders and strategies to prevent these late complications in patients with diabetes. Improved understanding of pathophysiology has the potential to lead to novel medical therapies in the future.

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Historical perspective

In 1936, Kimmelstiel and Wilson described the renal histology at autopsy in eight cases of which seven had diabetes, together with hypertension, albuminuria, edema, and renal failure and had the characteristic nodular lesions of diabetes mellitus. These findings were extended by other workers, [3,4] who confirmed the existence of a specific histopathology of the kidney in diabetes mellitus. Diffuse glomerulosclerosis was subsequently described and distinguished from the nodular form of Kimmelstiel and Wilson [5].

The introduction of percutaneous renal biopsies and electron microscopy in the 1950s rapidly led to a greater understanding of the disease. Studies confirmed that the earliest changes in the kidney in diabetes consisted of the accumulation of basement membrane–like material in the mesangium together with basement membrane thickening [6].

The most striking advances in DR relates to its treatment with retinal photocoagulation. The first use of photocoagulation in humans for retinal photocoagulation using the xenon arc lamp was by Meyer-Schwickerath in 1946. Several large clinical trials have helped define the epidemiology, natural history, and management strategies in DR [7–16].

Epidemiology

The epidemiology of DN has been best studied in patients with type 1 diabetes, because the time of clinical onset is usually known. Approximately 25% to 45% of these patients develop clinically evident disease during their lifetime [17–19]. The peak time to development of nephropathy in type 1 diabetes is between 10 and 15 years after the onset of disease. Importantly, patients who do not develop proteinuria after 20 to 25 years of diabetes have a very low subsequent risk of developing overt renal disease of only about 1% per year [17]. In patients with type 2 diabetes, the prevalence of progressive renal disease has previously been reported to be lower. Nephropathy develops in up to 50% of type 2 diabetic Pima Indians 20 years after diagnosis of type 2 diabetes, however, and 15% have progressed to ESRD by this time [20,21]. Importantly, proteinuria is a risk factor for cardiovascular disease and it is possible that previous studies underestimate the prevalence of DN in type 2 diabetes because many patients died of cardiovascular disease before developing ESRD.

Recent data suggest that the risk of nephropathy is equivalent in the two types of diabetes. Evidence in support of this hypothesis in one report were the observations that the time to proteinuria from the onset of diabetes and the time to ESRD from the onset of proteinuria were similar in type 1 and type 2 disease [22].

Diabetic retinopathy is more prevalent among patients with type 1 diabetes than type 2. Within 5 and 10 years of diagnosis, about 58% and
80%, respectively, have retinopathy. After 15 to 20 years of disease, more than 90% have some kind of retinopathy and approximately 60% have proliferative retinopathy. After greater than or equal to 20 years 99% have retinopathy and 53% have proliferative retinopathy. In comparison, more than 25% of patients with type 2 diabetes have retinopathy within 2 years of diagnosis. Sixty percent have some retinopathy and 5% have proliferative retinopathy greater than or equal to 20 years after diagnosis, far less than type 1 diabetes [23].

**Natural history and pathophysiology**

**Diabetic nephropathy**

The natural history of DN is complex, linked closely with the pathophysiology, and many changes in the kidney are currently not detectable in clinical practice. The course of DN is slow and fortunately modifiable by interventions used in clinical practice. Mogensen et al [24] propose a five-stage sequence for renal involvement (Table 1).

**Stage 1: glomerular hyperfiltration and renomegaly**

Even with good or fair glucose control, the GFR remains above control levels in 25% to 40% of patients. In this subgroup of hyperfiltering patients, reductions in the GFR and clinical nephropathy eventually develop at a much greater rate than in control patients with diabetes with normal GFR. Renal size and GFR are raised in newly diagnosed patients [25]. This raised GFR was shown to correlate closely with an increased glomerular capillary filtration surface area [26]. It has been suggested that patients with diabetes

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>Normal albumin excretion rate (AER &lt;20 μg/min)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Increased albumin excretion rate (AER 20–200 μg/min)</td>
</tr>
<tr>
<td>Incipient diabetic nephropathy</td>
<td>Persistent microalbuminuria (in at least two of three collections over 6 mo) ± hyperfiltration; blood pressure elevation</td>
</tr>
<tr>
<td>Early overt diabetic nephropathy</td>
<td>Clinical-grade proteinuria (AER &gt;200 μg/min in two of three collections within 6 mo or dipstick-positive proteinuria); hypertension</td>
</tr>
<tr>
<td>Advanced diabetic nephropathy</td>
<td>Progressive proteinuria; hypertension; declining glomerular filtration rate (decreased creatinine clearance, increased blood urea nitrogen and creatinine)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>Uremia; nephrotic syndrome; need for renal replacement therapy (transplantation or dialysis)</td>
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*Abbreviation: AER, albumin excretion rate in a timed specimen.*
with the highest GFR early in the course of their disease may be those most likely to develop DN [27,28]. There have been no prospective studies, however, demonstrating that patients with hyperfiltration progress to chronic renal failure at a greater or faster fashion than patients without hyperfiltration.

**Stage 2: early glomerular lesions**

There is mild thickening of glomerular basement membrane 18 to 24 months after the onset of type 1 diabetes and may be pronounced after 3.5 to 5 years [29]. Exercise-induced microalbuminuria is the only clinical evidence of renal involvement during this stage, which may extend from 4 or 5 to 15 years following the diagnosis of diabetes. Alteration in the molecular structure of components of the glomerulus and its basement membrane have also been suggested as primary pathogenetic mechanisms. Glycosylation of the basement membrane has been shown to occur and may result in the increased filtration of proteins [30]. A reduction in the negative charge of the basement membrane secondary to a degree in sialic acid and sulphated proteoglycans has been suggested as the basis for the proteinuria of DN. The repulsive electrostatic interaction with negatively charged plasma proteins, such as albumin, is reduced and so increased filtration of albumin may occur [31]. Vigstrup and Mogensen [32] published an article about microalbuminuria predicting proliferative DR. Mogensen [33] pointed out the importance of microalbuminuria as a predictor of clinical diabetic nephropathy (DN). Finally the same author proposed the five-stage sequence for renal involvement in type 1 diabetes mellitus [24].

**Stage 3: incipient diabetic nephropathy—stage of microalbuminuria**

Microalbuminuria, defined by a daily urinary albumin excretion rate of 20 to 200 µg/min, predicts renal functional deterioration and a poor outcome [34]. It is also associated with vascular damage in other organs.

**Stage 4: clinical nephropathy—macroalbuminuria, falling glomerular filtration rate**

The incidence of macroalbuminuria peaks in patients who have had diabetes for 15 to 20 years. Without intervention, the GFR in macroalbuminuric patients with type 1 diabetes falls at about 1 mL/min/mo [34,35]. Nephrotic syndrome is also very common.

**Stage 5: end-stage renal disease**

End-stage renal disease and its multiple complications and comorbid conditions occur after 20 to 30 years of diabetes in 30% to 40% of patients with type 1 diabetes. Uremic symptoms and signs are manifested at creatinine clearances that are higher than that in nondiabetic persons, and renal replacement therapy in suboptimal-treated individuals is needed within 2 to 3 years of the onset of nephrotic syndrome.
Diabetic retinopathy

In contrast, the natural history of DR is not as clearly defined, although the condition can be easily classified clinically (Table 2). The early stage of DR is characterized by loss of pericytes around capillaries in the retina. This is followed by development of weakness in the capillary wall that leads to capillary aneurysm formation (microaneurysm) and fluid leakage from capillaries as their walls become more permeable. Impaired vascular function gradually develops leading to areas of ischemia and infarction. In response to these changes local growth factors are secreted that contribute to new vessel proliferation.

Pathology

There are three major histologic changes in the glomeruli in DN: (1) mesangial expansion, (2) glomerular basement membrane thickening, and (3) glomerular sclerosis (Figs. 1–3) [36]. Glomerular sclerosis may have a nodular appearance called the “Kimmelstiel-Wilson lesion” and is often associated with hyaline deposits in the glomerular arterioles reflecting the insudation of plasma proteins, such as fibrin, immunoglobulins, and complement into the vascular wall [36,37].

The mesangial expansion and glomerulosclerosis do not always develop in parallel, suggesting that they may have somewhat different pathogenesis [37]. Mesangial expansion may be directly induced by hyperglycemia, by increased matrix production, or glycosylation of matrix proteins. In vitro studies have demonstrated that hyperglycemia stimulates mesangial cell matrix formation [37,38].

Nonproliferative DR is characterized by structural abnormalities of the retinal vessels (capillaries primarily, although venules and arterioles also

<table>
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<th>Classification</th>
<th>Characteristics</th>
<th>Impact on vision</th>
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<tbody>
<tr>
<td>Background (nonproliferative) retinopathy</td>
<td>Microaneurysms; venous dilatation; hemorrhages; exudates</td>
<td>None</td>
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<tr>
<td>Background retinopathy with maculopathy</td>
<td>Macular edema</td>
<td>May impair vision</td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>Neovascularization (pathognomonic feature); fibrous proliferation; preretinal hemorrhage; vitreous hemorrhage</td>
<td>Vision already affected at this stage</td>
</tr>
<tr>
<td>Advanced diabetic eye disease</td>
<td>Vitreous opacities (hemorrhage and fibrous tissues) Retinal detachment</td>
<td>Vision already affected at this stage</td>
</tr>
<tr>
<td>Involutional retinopathy</td>
<td>Residual scarring from previously active proliferative retinopathy</td>
<td>Vision already affected at this stage</td>
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may be involved); varying degrees of retinal nonperfusion; retinal edema; lipid exudates; and intraretinal hemorrhages (Figs. 4–6). Proliferative DR may include any of the previously mentioned changes with additional findings of optic disc or retinal or iris neovascularization. Tractional or retinal neovascularization may cause vitreous hemorrhages (Fig. 7). Vascular endothelial growth factor (VEGF) is a potent angiogenic and mitogenic molecule; increased VEGF is present in the retina of diabetic patients. It acts as a permeability factor and is implicated in increased amounts of vascular leakage and in the initiation of tumor angiogenesis [39–41].

Fig. 1. Normal glomerulus (Hematoxylin-eosin stain, ×100).

Fig. 2. Diffuse and nodular glomerulosclerosis (Kimmelstiel-Wilson lesion; Periodic acid Schiff stain, ×40).
Pathogenesis

The pathogenesis of both DN and DR is complex and multiple factors are involved in the process. Major risk factors for DN include the following:

- Hypertension
- Poor glycemic control
- Ethnicity (African American, Mexican American, and Pima Indians)
- Genetic susceptibility
- Increased glomerular filtration rate
- Increased plasma prorenin activity
- Increased sodium-lithium and sodium-hydrogen countertransport

Furthermore, there is a complex interaction of these factors and the presence of one may exacerbate the effects of another factor. First outlined are factors that are common to both conditions and then discussed are factors that may be specific to any one of the complications (Fig. 8).
Abnormalities related to hyperglycemia

Several epidemiologic and large prospective clinical studies have shown a strong association between glycemic control and diabetic microvascular complications. Glycemia-related vascular damage has been hypothesized to be mediated through various biochemical pathways including the hexosamine pathway, the advanced glycation end-product formation pathway, and the diacylglycerol (DAG)–protein kinase C (PKC) pathway. All seem to be caused by overproduction of superoxide by the mitochondrial electron-transport chain. The superoxide partially inhibits the glycolytic enzyme glyceraldehydes phosphate dehydrogenase, thereby diverting upstream metabolites from glycolysis into the four major glucose-driven signaling pathways causing hyperglycemic damage (Fig. 9) [40,42].

Glycosylation end-products, oxidative stress, and protein kinase C

Increased activation of the DAG-PKC signal transduction pathway has been identified in vascular tissues from diabetic animals, and in vascular cells exposed to elevated glucose. Vascular abnormalities associated with glucose-induced PKC activation leading to increased synthesis of DAG include altered vascular blood flow, extracellular matrix deposition, basement membrane thickening, increased permeability, and neovascularization [43].

Recent studies have yielded clues that may link hyperglycemia, pericyte death, and DR. Apoptosis of retinal capillary pericytes and, to a much lesser
extent, retinal capillary endothelial cells, has been demonstrated in humans who have early DR, but not in nondiabetic control patients [44,45]. Pericyte glutathione content, a basic defense against peroxidation, becomes depleted in high-glucose conditions [46]. During periods of glucose fluctuation, genes that encode products that regulate pericyte survival and death are up-regulated [47].

It seems that a high concentration of glucose followed by a large glucose fluctuation may be a death signal for retinal capillary pericytes. This apoptosis leads to a cascade of events that result first in background DR, and then with more extensive loss of pericytes and damage to endothelial cells and with a release of more factors (eg, transforming growth factor [TGF]-β), into the retinal milieu, an induction of distant phenomena occurs (eg, proliferative changes of the venular endothelial cells, proliferative diabetic retinopathy [PDR]).

![Fig. 7. Neovascularization (proliferative retinopathy).](image)

![Fig. 8. Pathologic processes leading to glomerular injury and proteinuria. AGE, advanced glycation end-product; Ang, angiotensin.](image)
Glycosylation of tissue proteins also may contribute to the development of DN and other microvascular complications. In chronic hyperglycemia, some of the excess glucose combines with free amino acids on circulating or tissue proteins. This nonenzymatic process initially forms reversible early glycosylation products and later irreversible advanced glycosylation end-products by an Amadori rearrangement.

Circulating advanced glycation end-product levels are increased in diabetics, particularly those with renal insufficiency, because advanced glycosylation end-products are normally excreted in the urine [48]. The net effect is tissue accumulation of advanced glycosylation end-products, in part by crosslinking with collagen, which can contribute to the associated renal and microvascular complications. Activation of cytokines may be another factor involved in the matrix accumulation in DN [49–51]. As an example, hyperglycemia increases the expression of TGF-β in the glomeruli and of matrix proteins specifically stimulated by this cytokine [51,52]. TGF-β may contribute to both the cellular hypertrophy and enhanced collagen synthesis that are seen in DN [53]. The administration of an angiotensin-converting enzyme (ACE) inhibitor to patients who have type 1 diabetes and nephropathy lowers serum concentrations of TGF-β [54]. An inverse correlation has been found between decreased TGF-β levels and renoprotection, as determined by changes in the glomerular filtration over time.

It has been proposed that activation of PKC by hyperglycemia contributes to the renal disease and other vascular complications of diabetes [55]. Before the discussion of its role, it is helpful to review the biochemistry and action of protein kinases. The reversible phosphorylation of proteins is the principal means of governing protein activity within cells. Protein kinases belong to a large family of enzymes that contain a similar 250–amino acid catalytic (kinase) domain but differ according to the amino acids on either side of the kinase domain. PKC activity is increased in glomeruli, retina, aorta, and heart of diabetic animals. This elevation in activity is probably caused by enhanced de novo synthesis of DAG, a major endogenous activator of PKC.

A role for PKC in the pathogenesis of DN is suggested by the results of several animal experiments. First, PKC is activated in glomeruli isolated from diabetic rats [56]. Second, activated PKC (especially the activated beta isof orm) in glomerular epithelial cells of induced diabetic rats participate in

Fig. 9. Potential mechanism by which hyperglycemia can cause tissue damage. Hyperglycemia-induced mitochondrial superoxide overproduction partially inhibits the glycolytic enzyme GAPDH, thereby diverting upstream metabolites from glycolysis into glucose-driven signaling pathways of glucose overuse. AGE, advanced glycation end-product; DAG, diacylglycerol; DHAP, dihydroxyacetone phosphate; GAPDH, glyceraldehyde phosphate dehydrogenase; GFAT, glutamine fructose-6-phosphate amidotransferase; PKC, protein kinase C; UDP, uridine diphosphate. (Adapted from Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, et al. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med 2003;9:294–9; with permission.)
the glycated albumin-induced stimulation of basement membrane type IV collagen production by glomerular endothelial cells [57].

Therapies aimed at lower PKC activity are in development. As an example, treatment of diabetic rats with \(d-\alpha\)-tocopherol, which inhibits PKC activation, prevents glomerular hyperfiltration and minimizes the development of proteinuria (2.4 versus 9.1 mg/d in control diabetic rats, versus 1.2 mg/d in nondiabetic rats) [58,59]. Preferential activation of the PKC beta isoform by elevated glucose is reported to occur in a variety of vascular tissues. This has led to the development of LY333531, a PKC beta isoform specific inhibitor, which has shown potential in animal models to be an orally effective and nontoxic therapy able to produce significant improvements in DR, DN, neuropathy, and cardiac dysfunction [43]. Additionally, the antioxidant vitamin E has been identified as an inhibitor of the DAG-PKC pathway, and shows promise in reducing vascular complications in animal models of diabetes. Given the overwhelming evidence indicating a role for PKC activation in contributing to the development of diabetic vascular complications, pharmacologic therapies that can modulate this pathway, particularly with PKC isoform selectivity, show great promise for treatment of vascular complications, even in the presence of hyperglycemia [58–61].

**Aldose reductase**

Aldose reductase is an enzyme that converts sugars into their respective alcohols. For example, glucose is converted into sorbitol and galactose is converted into galactitol. Because sorbitol and galactitol cannot easily diffuse out of cells, their intracellular concentration increases. Osmotic forces then cause water to diffuse into the cell, which results in electrolyte imbalance. The resultant damage to lens epithelial cells, which have a high concentration of aldose reductase, is responsible for the cataracts seen in children, in experimental animals with galactosemia, and in animals with experimental diabetes mellitus [62]. In addition, secondary metabolic changes in the target tissue, such as depletion of myoinositol, lead to tissue damage. Because aldose reductase also is found in high concentration in retinal pericytes and Schwann cells, some investigators suggest that DR and DN may be caused by aldose reductase–mediated damage. Strong support for this theory is that aldose reductase inhibitors inhibit both cataract formation and pericyte loss in experimental animals. Despite these theoretic benefits, however, clinical trials have failed to show a reduction in the incidence of DR or of DN by aldose reductase inhibitors, possibly because an effective aldose reductase inhibitor that has few systemic side effects has yet to be developed [62].

**Abnormalities independent of hyperglycemia**

**Growth factors**

Interest in the role of growth factors, independent of glycemia, in DN and DR stem from the fact that growth of vascular and matrix tissue is an important component of the pathology.
In the kidney, growth hormone has been implicated in the early stage of hypertrophy and hyperfiltration. As discussed later, other growth factors stimulated by angiotensin II may play a role in the increase in intraglomerular matrix hypertrophy. Angiotensin II itself has direct and potent cellular growth-promoting actions [63]. In addition, it stimulates production of important growth factors, such as TGF-β. The latter plays a key role in extracellular matrix formation in the mesangium of the kidney.

Activation of the renin-angiotensin system also leads to a selective constriction of the efferent arteriole (compared with the afferent one). This leads to an increase in intraglomerular pressure, an important contributor to renal damage. Indeed, the selective dilatation of the efferent arterioles has been suggested as a major factor in the greatly beneficial effects of ACE inhibitors and angiotensin receptor blockers in DN.

Furthermore, there is a decreased prevalence and possibly a regression of DR in patients with growth hormone deficiency. Growth hormone may play a causative or at least an important supportive role in the development and progression of diabetic vascular complications. Poulsen noted reversal of florid DR in a woman who had postpartum hemorrhagic necrosis of the pituitary gland (panhypopituitarism). More recently, growth hormone deficiency was found to be somewhat protective against retinopathy [64]. Administration of insulin-like growth factor also has been associated with retinal changes, although these are not entirely specific for DR.

It has been recently recognized that vasoproliferative factors, released by the retina itself, retinal vessels, or the retinal pigment epithelium, which may induce neovascularization. Vascular endothelial growth factor, which inhibits the growth of retinal endothelial cells in vitro, has recently been implicated in DR [65] and has also been found to be increased in the vitreous fluid of patients with DR [66].

### Risk factors and clinical predictors of diabetic nephropathy and retinopathy

**Glycemic control**

Diabetic nephropathy is more likely to develop in patients with poor glycemic control. Patients with type 1 diabetes whose hemoglobin A₁c concentration is maintained below 8.1% are at much lower risk for renal disease [21]. Randomized clinical trials have confirmed the predictive value of poor control compared with good control in determining the risk of nephropathy and retinopathy. The United Kingdom Prospective Diabetes Study (UKPDS) of patients with type 2 diabetes found that fewer patients treated with intensive versus conventional therapy had progression of microalbuminuria (27% versus 39%) and proteinuria (7% versus 13%) over 15 years of follow-up [67]. The Diabetes Control and Complications Trial (DCCT) showed that combined, intensive therapy reduced the
occurrence of microalbuminuria (urinary albumin excretion of \( \geq 40 \text{ mg per 24 hours} \)) by 39% and that of albuminuria (urinary albumin excretion of \( \geq 300 \text{ mg per 24 hours} \)) by 54% [68].

The DCCT showed 76% reduction in the rate of development of any retinopathy and an 80% reduction in progression of established retinopathy versus those with conventional control. These risk reductions, achieved at a median hemoglobin A\(_1c\) level difference of 9.1% for conventional treatment versus 7.3% for intensive treatment, have been maintained through 7 years of continued follow-up in the Epidemiology of Diabetes Interventions and Complications study, even though the difference in mean hemoglobin A\(_1c\) levels of the two former randomized treatment groups was only 0.4% 1 year after conclusion of the DCCT (8.3% in the former conventional treatment group versus 7.9% in the former intensive treatment group); continued to narrow; and became statistically nonsignificant by 5 years (8.1% versus 8.2%, \( P = .09 \)). The further rate of progression of complications from their levels at the end of the DCCT remains less in the former intensive treatment group. The benefits of 6.5 years of intensive treatment extend well beyond the period of its most intensive implementation. Intensive treatment should be started as soon as is safely possible after the onset of type 1 diabetes mellitus and maintained thereafter, aiming for a practicable target hemoglobin A\(_1c\) level of 7% or less [66,69,70].

Wisconsin epidemiologic study of DR was a population-based study in southern Wisconsin conducted to determine the prevalence and severity of DR and associated risk variables. It showed a positive correlation between severity of retinopathy and high levels of glycosylated hemoglobin after 10 years of diabetes [10].

For patients with advanced retinopathy, however, even the most rigorous control of blood glucose may not prevent progression. Even patients attaining normoglycemia by pancreatic transplantation continue to show progression of retinopathy [71].

**Duration of disease**

In various randomized controlled trials, the total duration of disease has been found to be the strongest predictor of development and progression of DR [72]. In the Wisconsin epidemiologic study of DR, prevalence in younger-onset patients with diabetes was 8%, 25%, 60%, and 80% at 3, 5, 10, and 15 years after diagnosis, respectively [10].

**Blood pressure**

Some research indicates that elevated systolic blood pressure is a moderate risk factor for both DN and DR, more so for the latter [72]. In UKPDS trial tight blood pressure control was shown to cause 34% reduction in progression of retinopathy and a 47% reduced risk of deterioration in visual
acuity of three lines in association with a 10/5 mm Hg reduction in blood pressure [13]. The appropriate Blood Pressure Control in Diabetes Trial was conducted to determine whether intensive blood pressure control (diastolic blood pressure goal of 75 mm Hg) offers additional benefit over moderate control (diastolic blood pressure between 80 and 89 mm Hg). Intensive therapy showed a lower incidence of deaths; however, there was no difference with regards to progression of DR [73].

Genetics

The increased synthesis of angiotensin II plays an important role in initiation and progression of DN by affecting hemodynamic and non-hemodynamic mechanisms [74]. Studies have shown that an inversion (I)-deletion (D) polymorphism of the ACE gene (ACE/ID) is associated with the level of circulating ACE and with an increased risk of coronary heart disease in nondiabetic patients [75]. Yoshida et al [76] followed 168 proteinuric patients with type 2 diabetes for 10 years and found in an analysis of the clinical course of the three ACE genotypes that most patients with the DD genotypes (95%) progressed to ESRD within 10 years. Two recent studies have confirmed that the D allele has a deleterious effect on renal function in patients with type 2 diabetes [77,78].

Several studies have shown that the likelihood of developing DN is markedly increased in patients with a diabetic sibling or parent who has DN; these observations have been made in both type 1 and type 2 diabetes [79–81]. One report, for example, evaluated Pima Indians in which two successive generations had type 2 diabetes [79]. The likelihood of the offspring developing overt proteinuria was 14% if neither parent had proteinuria, 23% if one parent had proteinuria, and 46% if both parents had proteinuria.

One component of the genetic risk may be the ACE gene genotype. In patients with type 2 diabetes, the DD polymorphism has been associated with an increased risk for the development of DN, more severe proteinuria, a greater likelihood of progressive renal failure, and enhanced mortality on dialysis [76,82,83]. A critical review of 19 studies examining a possible link between the ACE gene genotype and DN failed to confirm an association among whites with either type 1 or type 2 diabetes, but could not exclude a possible association in Asians [84]. Unfortunately, because of poor methodology, no definite conclusions could be drawn.

An enhanced risk may also be caused by inheritance of one allele of the aldose reductase gene, the rate-limiting enzyme for the polyol pathway. In a controlled study of patients with type 1 diabetes, homozygosity for the Z-2 allele was significantly associated with an odds ratio of 5.25 for the presence of nephropathy [85].

Many patients with salt-sensitive essential hypertension have an elevation in red cell sodium-lithium countertransport; increased sodium-hydrogen
exchange has also been linked to the development of hypertension. These abnormalities are thought to be markers for enhanced sodium transport at sites that might induce a rise in blood pressure, such as the kidney or vascular smooth muscle. Some studies have suggested that type 1 diabetics with nephropathy have higher rates of sodium-hydrogen exchange and red cell sodium-lithium countertransport than those without renal disease [86–88]. Sodium-hydrogen exchange activity is concordant among type 1 diabetic siblings, suggesting that this activity is genetically determined [89].

Glomerular filtration rate

Approximately half of patients with type 1 diabetes of less than 5 years duration have an elevated GFR that is 25% to 50% above normal. Those patients with glomerular hyperfiltration seem to be at increased risk for diabetic renal disease [90,91]. In one prospective study, for example, patients with type 1 diabetes and a GFR above 125 mL/min had a risk of developing microalbuminuria within 8 years of approximately 50% versus only 5% in patients with a lower GFR that was similar to that seen in nondiabetics [90].

The glomerular hyperfiltration in type 1 diabetics is typically associated with glomerular hypertrophy and increased renal size [92]. The association between these hemodynamic and structural changes and the development of DN may be related both to intraglomerular hypertension (which drives the hyperfiltration) and to glomerular hypertrophy (which also increases wall stress). Therapy aimed at reversing these changes (with aggressive control of plasma glucose concentration early in the course of the disease [92], dietary protein restriction, and antihypertensive therapy) may slow the rate of progression of the renal disease.

The findings in type 2 diabetes are somewhat different. Up to 45% of affected patients initially have a GFR that is more than 2 standard deviations above age-matched non-diabetic and obese controls [93,94]. The degree of hyperfiltration (averaging 117 to 133 mL/min), however, is less than that seen in type 1 diabetics. Type 2 diabetics are also older and more likely to have atherosclerotic vascular disease, which limits increases in both glomerular filtration and glomerular size [95].

Ethnicity

The incidence and severity of DN are increased in blacks (threefold to sixfold compared with whites), Mexican-Americans, and Pima Indians with type 2 diabetes [20,96,97]. This observation in such genetically disparate populations suggests a primary role for socioeconomic factors, such as diet, poor control of hyperglycemia, hypertension, and obesity [98].

As an example, there seems to be an important association between hypertension and disease progression in black patients with type 2 diabetes. A cross-sectional study found that GFR was normal in patients who were
normotensive; in comparison, hypertension was associated with a decline in renal function, particularly if it developed after the onset of diabetes and the patient had been diabetic for more than 10 years [99]. It is not clear, however, if the hypertension worsened the renal disease or was simply a marker for more severe renal involvement.

The importance of genetic influences, however, in the racial propensity to DN cannot be excluded. Even when adjustments are made for the increased incidence of hypertension and lower socioeconomic status in blacks, there still seems to be as much as a 4.8-fold increase in the risk of ESRD caused by DN in blacks [97]. This seems to occur only in type 2 diabetes, with no increase in risk seen with type 1 diabetes.

**Relationship between diabetic nephropathy and retinopathy**

Patients with nephropathy and type 1 diabetes almost always have other signs of diabetic microvascular disease, such as retinopathy and neuropathy [18,19]. By the time advanced retinopathy has occurred, there are histologic changes in the glomeruli and increased protein excretion that is at least in the microalbuminuric range [100]. Renal disease as evidenced by proteinuria, elevated blood urea nitrogen, and elevated blood creatinine is an excellent predictor of the presence of retinopathy [101]. Even patients who have microalbuminuria are at high risk of developing retinopathy [102]. Similarly, 35% of patients symptomatic for retinopathy have proteinuria, elevated blood urea nitrogen, or elevated creatinine.

The relationship between DN and DR is less predictable in type 2 diabetes. In one study of 35 patients with diabetes and significant proteinuria (>300 mg/d), 27 (77%) were found to have DN [103]. DR was present in 15 (56%) of the 27 and in 0 of the 8 individuals without DN, thereby resulting in a sensitivity and specificity of 40% and 100%, respectively. Further analysis of some of these patients plus additional type 2 diabetics with proteinuria found that, among those without retinopathy, approximately 30% did not have DN on renal biopsy [104].

Type 2 diabetics with marked proteinuria and retinopathy most likely have DN, whereas those without retinopathy have a high incidence of nondiabetic glomerular disease.

**Pregnancy**

In women who begin a pregnancy without retinopathy, the risk of developing nonproliferative DR is about 10%. Further, those with nonproliferative DR at the onset of pregnancy and those who have or who develop systemic hypertension tend to show progression, with increased hemorrhages, cotton wool spots, and macular edema [105]. Fortunately, usually some regression occurs after delivery. About 4% of pregnant women who have nonproliferative DR progress to PDR. Those with untreated PDR at the onset of pregnancy frequently do poorly unless they are treated using panretinal photocoagulation. Finally, patients who have
previously had successfully treated PDR usually do not worsen during pregnancy. Women who begin pregnancy with poorly controlled diabetes, however, but who then are suddenly brought under strict control frequently have severe, rapid worsening of their retinopathy and do not always recover after delivery [105].

Other renal diseases

Proteinuria in diabetes mellitus is occasionally caused by a glomerular disease other than DN. As examples, membranous nephropathy, minimal change disease, IgA nephropathy, Henoch-Schönlein purpura, thin basement membrane disease, and a proliferative glomerulonephritis have all been described [19,95,104,106–113].

Major clinical clues suggesting nondiabetic kidney disease include onset of proteinuria less than 5 years from the documented onset of diabetes, acute onset of renal disease, presence of an active urine sediment containing red cells and cellular casts, and the absence of DR or DN. Lack of retinopathy in type 2 diabetes does not preclude DN, however, which remains the most likely diagnosis [19,103,104].

Diagnosis

Diagnosis of diabetic nephropathy

Guidelines for systematic screening have been developed because patients with nephropathy are often asymptomatic and because a number of effective intervention strategies can slow disease progression (Table 3).

Screening for DN needs to be a routine component of diabetes care. The American Diabetes Association recommends yearly screening for individuals with type 2 diabetes and yearly screening for those with type 1 diabetes after 5 years’ duration of disease (but not before puberty). Several screening techniques are available: the albumin:creatinine ratio from a random spot urine collection, a 24-hour urine collection for albuminuria and creatinine (allowing calculation of creatinine clearance as well), or a timed (eg, overnight or 3- to 4-hour) urine collection are all acceptable. Positive results need to be confirmed with a second measurement because of the high variability in albumin excretion in people with diabetes. Use of urine dipsticks for microalbuminuria (on fresh morning specimens) is reasonable for initial screens, but these findings are semiquantitative, and positive tests should be followed-up by a 24-hour or timed urine collection. Microalbuminuria is considered to be present if urinary albumin excretion is 30 to 300 mg per 24 hours (equivalent to 20–200 µg/min on a timed specimen or 30–300 mg/g creatinine on a random sample) (Fig. 10). Short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient
elevations in urinary albumin excretion. There is also marked day-to-day variability in albumin excretion, so at least two to three collections done in a 3- to 6-month period should show elevated levels before a patient is designated as having microalbuminuria and treatment is initiated.

Detection of diabetic retinopathy

Guidelines for systematic screening have been developed because patients with retinopathy are often asymptomatic, and photocoagulation treatment is more effective in reducing visual loss when applied at specific, frequently asymptomatic stages of retinopathy. Regular dilated eye examinations are effective in detecting and treating vision-threatening DR. Current guidelines suggest that diabetic patients have an initial dilated and comprehensive eye examination by an ophthalmologist shortly after the diagnosis of diabetes is made in patients with type 2 diabetes, and within 3 to 5 years after the onset of type 1 diabetes (but not before age 10 years) [114]. Any patient with visual symptoms or abnormalities should be referred for ophthalmologic evaluation.

Subsequent examinations for both type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist who is experienced in diagnosing the presence of DR and is knowledgeable about its management [114]. More frequent examinations are needed especially in patients who have progressive disease and severe nonproliferative disease. Women with diabetes should have a comprehensive eye examination when planning pregnancy and during the first trimester of pregnancy and should be followed closely during pregnancy.

Patients with any level of macular edema, severe nonproliferative retinopathy, or any proliferative retinopathy require the prompt care of an ophthalmologist who is knowledgeable and experienced in the management and treatment of DR.

The most sensitive way to detect retinopathy is by fundus photography through a dilated pupil, involving seven stereoscopic 30-degree standard fields. Proper fundus photography requires a photographer skilled in

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### Table 3
Interpretation of urinary albumin excretion (based on different assessment methods)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Urinary AER (mg/min)</th>
<th>Urinary AER (mg/24 hr)</th>
<th>Urine albumin: creatinine ratio (mg/g)</th>
<th>Morning urine albumin concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;20</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>20–200</td>
<td>30–300</td>
<td>30–300</td>
<td>30–300</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;200</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

**Abbreviation:** AER, albumin excretion rate in a timed specimen.
obtaining the rigorously defined and technically challenging photographic fields of appropriate quality plus a reader skilled in the interpretation of the photographs. If either of these components is not available or does not meet the defined standards, a dilated ophthalmic examination by an experienced ophthalmologist is recommended. Such examinations should be performed by ophthalmologists because the difficulty in assessing DR is such that in one study the rates of serious errors in assessment were 52% for general internists, 50% for medical residents, and 33% for diabetologists but were only 9% for general ophthalmologists and 0% for retinal specialists [115].

New screening technologies include dynamic light scattering [116], Raman spectroscopy [117], autofluorescence imaging [118], and Doppler flowmetry [119]. All use laser light to measure various molecular structures and physiologies to detect abnormalities before the advanced stages of histopathology. These can aid in earlier diagnosis and treatment.

Teleophthalmology is an emerging new tool for diagnosis. Gomez-Ulla et al [120] obtained retinal images and sent by internet for grading by an

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Fig. 10. Screening for microalbuminuria. (From Molith M, Franz M, Keane W, Megensen CE, Parring H, Steffes M. Clinical practice recommendations: diabetic nephropathy. Diabet Care 2003;26(Suppl 1):S96; with permission.)
ophthalmologist to a remote reference center. The results were compared with findings by an ophthalmologist on direct eye examination and found to have 100% agreement.

Microalbuminuria and proteinuria

Microalbuminuria and proteinuria are part of the spectrum of clinical manifestation of DN. Microalbuminuria is defined as the presence of urinary albumin above the normal but below the detectable range with the conventional urine dipstick methodology. It is recognized as a complication of diabetes because of changes in the kidney secondary to hyperglycemia. In diabetic patients, this consists of a urinary albumin excretion rate of 20 to 200 μg/min (30–300 μg/mg of creatinine on a spot urine sample or 30–200 mg per 24 hours), because rates within this range have been shown to predict the progression of DN. In contrast the terms “proteinuria,” “albuminuria,” and “overt nephropathy” are used when the urine dipstick is positive or the albumin excretion is greater than 200 mg per 24 hours. The difference between microalbuminuria and overt proteinuria is essentially a matter of degree. Microalbuminuria may be transient or reversible in its early stages, however, whereas proteinuria usually progresses over a variable period to ESRD.

Several studies have demonstrated that microalbuminuria is a risk factor for cardiovascular events [121–126]. Recent data suggest that it may occur even in nondiabetics, may be a precursor of cardiovascular disease, and may be related to insulin resistance [127–130]. Microalbuminuria may precede and predict the development of type 2 diabetes [131], and the progression of microalbuminuria is associated with a worsening prognosis for cardiovascular disease risk [124].

Albuminuria clusters with other cardiovascular disease risk factors, particularly dyslipidemia, left ventricular hypertrophy, and the absence of nocturnal drops in both systolic and diastolic blood pressures. Elevated systolic blood pressure is a significant determining factor in the development of microalbuminuria and the progression of albuminuria in type 2 diabetes. Data also suggest that microalbuminuria reflects increased leakage of albumin across the endothelial barrier and is a clinically easily measurable indicator of endothelial integrity. Indeed, patients with microalbuminuria are likely to have several biochemical and functional abnormalities of endothelial function.

Clinical disease progression

The likelihood of progression from microalbuminuria to overt nephropathy (positive urine dipstick for protein) is determined by the type and duration of diabetes. In type 1 diabetics, clinical renal involvement begins 10 to 15 years after the diagnosis of diabetes; patients without proteinuria after 20 years have a risk of developing overt renal disease of 1% per year [132].
Patients who progress are more likely to have higher hemoglobin A1c values and a higher blood pressure than nonprogressors [133,134]. A retrospective study measured both albumin excretion and glycemic control in 1613 patients with type 1 diabetes [134]. The risk of having microalbuminuria increased abruptly at hemoglobin A1c value above 8.1%. In a prospective report, multivariate analysis of 1134 patients with type 1 diabetes found that higher values for hemoglobin A1c were independent risk factors for progression to microalbuminuria [135]. Progressors also had higher systolic and diastolic blood pressures (123/75 mm Hg versus 118/73 mm Hg for nonprogressors).

Progression from microalbuminuria to overt nephropathy within a 10-year period occurs in 20% to 40% of white patients with type 2 diabetes [136,137]. Risk factors contributing to progression include hyperglycemia, hypertension, and cigarette smoking. Other studies of Pima Indians and Israeli patients with type 2 diabetes have found a 4- to 5-year rate of progression to overt proteinuria of 37% to 42% [138,139]. A 4-year follow-up of 34 patients with overt proteinuria found a mean loss in GFR of 0.93 mL/min/mo, a rate similar to that observed in patients with type 1 diabetes [138].

Management

Prevention

Strong clinical trial data suggest that both DN and DR can be prevented by good glycemic control. In addition to glycemic control data suggest that good blood pressure control may also decrease the onset of DR and DN. Furthermore, the development of microalbuminuria is delayed by ACE inhibitors [140,141].

The DCCT, a randomized, multicenter, controlled clinical trial, demonstrated that intensive treatment of type 1 diabetes-decreased the progression of nephropathy and retinopathy. The incidence of microalbuminuria was significantly reduced by 39% in three combined cohorts, by 34% in the primary-prevention cohort, and by 43% in the secondary-intervention cohort [68].

The UKPDS, a randomized, multicenter, controlled clinical trial, demonstrated that a policy of intensive treatment with goal of meticulous glycemic control could decrease complications of type 2 diabetes. Patients assigned to the intensive policy A1c of 7% had a significant 25% risk reduction in microvascular end points (P < .01) compared with those in the conventional policy A1c of 7.9%. At 9, 12, and 15 years follow-up the risk reduction in the appearance of microalbuminuria was 24%, 33%, and 30%, respectively [67].

The benefit of antihypertensive therapy with an ACE inhibitor in type 1 diabetes can be demonstrated early in the course of the disease when microalbuminuria is the only clinical manifestation. In one study, the administration of an ACE inhibitor to normotensive type 1 diabetics with microalbuminuria decreased both albumin excretion and at 2 years
progression of disease when compared with patients treated on placebo [142,143]. The Heart Outcomes Prevention Evaluation (HOPE) study, an international randomized trial, was designed to evaluate the effects of the ACE inhibitor ramipril and vitamin E in patients at high risk for cardiovascular events. Ramipril use was associated with a significant 25% reduction in risk for the composite end point of myocardial infarction, stroke, or cardiovascular death after a median follow-up period of 4.5 years. The Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE, a sub-study in this patient population, showed that ramipril treatment was associated with a decreased risk of development of overt nephropathy[144].

**Treatment of diabetic nephropathy**

Studies of blood pressure control and the evolution and progression of DN have focused on ACE inhibitors or more recently on angiotensin receptor blockers. The value of ACE inhibitors in patients with established DN was demonstrated in a landmark study with captopril [145]. Four hundred nine patients with overt proteinuria and creatinine less than or equal to 2.5 were randomized to therapy with either captopril or placebo. With equivalent blood pressure control, patients treated with captopril had a slower rate of increase in creatinine concentration and a lesser likelihood of progressing to ESRD or death [145,146]. Beneficial response to captopril, which was seen in both hypertensive and normotensive subjects, is consistent with smaller studies, which suggested that antihypertensive therapy, particularly with an ACE inhibitor, slowed the rate of progression in DN [141,147]. Captopril treatment was associated with a 50% reduction in the risk of the combined end points of death, dialysis, and transplantation that was independent of blood pressure.

There has been less information on the effect of antihypertensive therapy with ACE inhibitors in patients with nephropathy caused by type 2 diabetes, although a similar benefit seems to be present. More data from large clinical trials are available on the efficacy of angiotensin receptor blockers. In the UKPDS each 10 mm Hg reduction in systolic pressure was associated with a 12% risk reduction in diabetic complications ($P < .001$); the lowest risk occurred at a systolic pressure below 120 mm Hg. There was no difference between captopril and atenolol in progression of complications [148]. Similar results were found in the ALLHAT study [149]. HOPE, however, showed decreased proteinuria with ACE inhibitors [144].

Brenner et al [150] assessed the role of the angiotensin II receptor antagonist losartan in 1513 patients with type 2 diabetes and nephropathy in a randomized, double-blind study comparing losartan with placebo, both taken in addition to conventional antihypertensive treatment over a mean of 3.4 years. Losartan significantly reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25%) and ESRD (risk reduction, 28%) but had no effect on the rate of death. The benefit exceeded that
attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction, 32%). The level of proteinuria declined by 35% with losartan. Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and it was generally well tolerated.

In another large study, the angiotensin II receptor blocker irbesartan was effective in protecting against the progression of nephropathy caused by type 2 diabetes. This protection was independent of the reduction in blood pressure it causes [151]. Irbesartan was also shown to be renoprotective independently of its blood pressure lowering effect in patients with type 2 diabetes and microalbuminuria, slowing the progression to overt proteinuria [152].

The CALM study was conducted to assess and compare the effects of candesartan or lisinopril, or both, on blood pressure and urinary albumin excretion in patients with microalbuminuria, hypertension, and type 2 diabetes. In this prospective, randomized, double-blind study there was a 4-week placebo run in period and 12 weeks monotherapy with candesartan or lisinopril followed by 12 weeks monotherapy or combination treatment. At 24 weeks the mean reduction in diastolic blood pressure with combination treatment (16.3 mm Hg, 13.6–18.9 mm Hg, \( P < .001 \)) was significantly greater than that with candesartan (10.4 mm Hg, 7.7–13.1 mm Hg, \( P < .001 \)) or lisinopril (mean 10.7 mm Hg, 8–13.5 mm Hg, \( P < .001 \)). Furthermore, the reduction in urinary albumin:creatinine ratio with combination treatment (50%, 36%–61%, \( P < .001 \)) was greater than with candesartan (24%, 0%–43%, \( P = .05 \)) and lisinopril (39%, 20%–54%, \( P < .001 \)). In conclusion, combination treatment was found to be well tolerated and more effective in reducing blood pressure [153].

The primary aim of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial was to compare the effects of fosinopril and amlodipine on serum lipids and diabetes control in non–insulin-dependent diabetes mellitus patients with hypertension. A total of 380 hypertensive diabetics were randomly assigned to open-label fosinopril (20 mg/d) or amlodipine (10 mg/d) and followed for up to 3.5 years. If blood pressure was not controlled, the other study drug was added. Both treatments were effective in lowering blood pressure [154]. Combination therapy is frequently used in clinical practice for optimal blood pressure control.

Once the plasma creatinine is elevated indicating low clearance the prognosis worsens significantly. Patients at this stage of nephropathy are difficult to manage because of the presence of other complications including cardiovascular disease. In addition, the pharmacokinetics of insulin and other medications change because of the decreased kidney metabolism and clearance. Metformin is contraindicated and thiazolidinediones become difficult to use because of fluid retention. Both hypoglycemia and hyperglycemia are frequent.
The management of ESRD caused by DN is beyond the scope of this article. Data suggest that early referral to a specialist experienced in managing such patients improves outcomes [155]. As the disease progresses patients should be prepared for dialysis. In general, patients have better outcomes with peritoneal than hemodialysis and better outcomes with transplantation than dialysis. For patients with type 1 diabetes a combined kidney pancreas transplant, apart from eliminating the need for insulin, leads to better outcomes than kidney transplantation alone.

Treatment of diabetic retinopathy

Medical therapy

The success of laser photocoagulation in treating DR is well established and medical therapy has very little role other than a supportive one. Nevertheless, several clinical trails have been performed to develop medical therapy. Although aspirin inhibits platelet secretion and aggregation, it does not influence the progression of retinopathy, affect visual acuity, or influence the incidence of vitreous hemorrhages [156]. The Ticlopidine Microangiopathy of Diabetes Study Group in France examined the effect of ticlopidine, an inhibitor of adenosine diphosphate–induced platelet aggregation, showing that was associated with a sevenfold decrease in microaneurysm count during 3 years of follow-up compared with placebo in insulin-treated patient with no benefit in non–insulin-treated patients [157]. This is only one study showing a statistical benefit, however, but it was not performed long enough to show a clinical benefit. It is not routinely prescribed in United States.

Surgical therapy

Several multicenter, prospective, randomized, controlled studies have demonstrated that intervention with laser photocoagulation surgery or vitrectomy may preserve vision in certain patients with DR. These studies are discussed next.

Panretinal photocoagulation

Panretinal photocoagulation is the treatment of choice for high-risk retinopathy. The Diabetic Retinopathy Study first established the benefit in treatment of eyes with high-risk criteria with proliferative retinopathy. Laser panretinal photocoagulation significantly reduced the likelihood that an eye with high-risk characteristics progresses to severe visual loss, up to greater than a 50% reduction in visual loss [7]. Eyes with high-risk characteristics are defined as those with neovascularization of the disk greater than half the disk area, those with any neovascularization of the disk and vitreous hemorrhage, or those with neovascularization elsewhere greater than half the disc area and vitreous or preretinal hemorrhage.
The mechanism of action of panretinal photocoagulation is still unknown. Some investigators have hypothesized that panretinal photocoagulation decreases the production of vasoproliferative factors by eliminating some of the hypoxic retina or by stimulating the release of antiangiogenic factors from the retinal pigment epithelium [158]. An alternative hypothesis is that chronic hypoxia stimulates neovascularization by causing vessel dilatation resulting in endothelial cell proliferation. By thinning the retina, panretinal photocoagulation increases oxygenation of the remaining retina as it enables an increased diffusion of oxygen from the choroid and so decreases vasodilatation [159]. Finally, others suggest that panretinal photocoagulation leads to an increase in vaso inhibitors by stimulating the retinal pigment epithelium to produce inhibitors of vasoproliferation [160].

The number of burns necessary to achieve these goals has not been established. Some retinal specialists believe that there is no upper limit to the total number of burns and that treatment should be continued until regression occurs [161]. The only prospective, controlled study, however, found that eyes that received supplementary treatment had no difference in reduction in risk factors or better visual acuity than did those that only received standard panretinal photocoagulation [162]. About two thirds of eyes with high-risk characteristics that receive panretinal photocoagulation have regression of their high-risk characteristics by 3 months after treatment.

**Photocoagulation for treatment of macular edema**

Patients who have macular edema have the best prognosis for improved vision if they have circinate retinopathy of recent duration or focal, well-defined leaking areas and good capillary perfusion surrounding the foveal avascular zone. Patients with an especially poor prognosis have dense lipid exudates in the center of the fovea. Other poor prognostic signs include diffuse edema with multiple leaking areas, extensive central capillary nonperfusion, increased blood pressure, and cystoid macular edema [163]. Nevertheless, the Early Treatment Diabetic Retinopathy Study Research Group (ETDRS) showed that even eyes with these adverse findings benefited from treatment when compared with control eyes [164].

Patz et al [163] was the first to show that argon laser photocoagulation decreases or stabilizes macular edema. Later, the ETDRS confirmed these results. The ETDRS defined clinically significant macular edema as retinal thickening involving the center of the macula, or hard exudates within 500 μm of the center of the macula or an area of macular edema greater than one disk area but within one disc diameter of the center of the macula.

The treatment strategy is to treat all leaking microaneurysms further than 500 μm from the center of the macula and to place a grid of 100 to 200 μm burns in areas of diffuse capillary leakage and in areas of capillary nonperfusion. After 3 years of follow-up, 15% of eyes with clinically significant macular edema had doubling of the visual angle as opposed to 32% of untreated
control eyes [164]. The ETDRS also showed that panretinal photocoagulation should not be given to eyes with clinically significant macular edema unless high-risk criteria are present [165]. An acceptable alternative treatment to the ETDRS strategy is a grid treatment [166].

Panretinal photocoagulation has significant complications: it often causes decreased visual acuity by increasing macular edema [167] or by causing macular pucker. Fortunately, the edema frequently regresses spontaneously over 6 months, but the visual field is usually moderately, yet permanently, decreased. Color vision and dark adaptation, which are often already impaired, are worsened by panretinal photocoagulation [168]. For this reason, panretinal photocoagulation is not recommended for patients with background DR, who should nevertheless be followed-up closely to detect any disease progression.

Vitrectomy

Vitrectomy, introduced by Machemer et al [169], plays a vital role in the management of severe complications of DR. The major indications are nonclearing vitreous hemorrhage, macular involving or threatening traction retinal detachment, and combined traction-rhegmatogenous retinal detachment. Less common indications are macular edema with a thickened and taut posterior hyaloid [170], macular heterotopia, epiretinal membrane, severe preretinal macular hemorrhage, and neovascular glaucoma with cloudy media.

Summary

There has been much progress in the understanding of the pathogenesis and pathophysiology of DN and DR. This has resulted in significant advances in treatment. In particular the blockade of the renin-angiotensin system for DN and laser photocoagulation for DR has resulted in decreasing long-term morbidity. Nevertheless, the impact of these complications remains significant and clinicians should remain vigilant. Regular screening as recommended by guidelines and prompt institution of treatment lead to further reductions in morbidity and mortality.

References


