# Diseases of Renal Microcirculation: Diabetic Nephropathy

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## Contents



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P. Lanzer (ed.), *PanVascular Medicine*, DOI 10.1007/978-3-642-37078-6_149

**Abstract**

The prevalence of diabetes mellitus and its long-term vascular complications are increasing worldwide. Diabetic nephropathy is one of the main microvascular complications of diabetes and is characterized by the development of persistent macroalbuminuria (i.e., a urinary albumin excretion [UAE] >300 mg/24 h) or proteinuria (i.e., a urinary protein excretion >0.5 g/24 h).

Characteristic glomerular changes of diabetic nephropathy include thickening of the glomerular basement membrane (GBM), mesangial expansion, and podocyte injury. Since type 1 and type 2 diabetic nephropathies share similar histologic characteristics as well as structural-functional relationships, one common classification is used to describe the pathologic classification of diabetic nephropathy for both type 1 and 2 diabetes.

Although UAE should rather be considered as a continuous variable rather than using specific cutoff values, we describe the clinical course of diabetic nephropathy based on the classic approach using three stages based on urinary albumin excretion (i.e., normoalbuminuria, microalbuminuria, and macroalbuminuria).

Diabetic nephropathy is a major independent risk factor for diabetes-related morbidity and mortality. However, a number of interventions are available that can reduce the risk of developing diabetic nephropathy and slow the progression hereof. Key treatment strategies that could reduce the incidence and progression of diabetic nephropathy include blood glucose control, blood pressure control, lipid-lowering therapy, and lifestyle interventions.

**Glossary of Terms**

**Albuminuria** Condition wherein too much albumin is present in urine.

**Atherosclerosis** A common form of arteriosclerosis in which fatty substances form a deposit of plaque on the inner lining of arterial walls.

**Diabetes mellitus** A metabolic disorder that is clinically characterized by hyperglycemia.

**Diabetic nephropathy** Diabetic kidney disease characterized by the presence of albuminuria or proteinuria.

**Dyslipidemia** A disorder of lipid metabolism, including overproduction or deficiency.

**End-stage renal disease** Late stage of kidney disease in which renal replacement therapy is needed.

**Glomerular hyperfiltration** An elevation in the glomerular filtration rate that can occur in various clinical conditions including diabetes mellitus.

**Hypertension** High blood pressure; systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

**Macroalbuminuria** Presence of large amounts of albumin in urine; urinary albumin excretion of >300 mg/day.

**Microalbuminuria** Presence of small amounts of albumin in urine; urinary albumin excretion of 30–300 mg/day.

**Normoalbuminuria** Presence of normal amounts of albumin in urine; urinary albumin excretion of <30 mg/day.

**Proteinuria** Condition wherein too much protein is present in urine.

## Epidemiology of Diabetes and Its Complications

### Diabetes and Its Complications

The incidence of diabetes mellitus, a metabolic disorder that is clinically characterized by hyperglycemia, has increased by 50 % over the past decade (Forbes and Cooper 2013; Danaei et al. 2011). In 2011, there are 366 million people with diabetes worldwide, and this number is expected to rise to 552 million by 2030 (Whiting et al. 2011).

Diabetes mellitus is associated with a number of complications, ranging from acute metabolic to long-term vascular complications. These

**Table 1** Overview diabetes-related complications

| | Long-term vascular complications | |
|---|---|---|
| Acute metabolic complications | Macrovascular complications | Microvascular complications |
| Ketoacidosis | Cardiovascular disease | Retinopathy |
| | Cerebrovascular disease | Nephropathy |
| | Stroke | Neuropathy |

vascular complications are, at least partly, a consequence of chronic hyperglycemia, which leads to damage of large blood vessels (i.e., *macrovascular complications*) as well as small blood vessels (i.e., *microvascular complications*) (Table 1).

## Macrovascular Complications

The main macrovascular complication of diabetes is cardiovascular disease, predominantly caused by atherosclerosis, resulting in coronary artery disease often manifesting as myocardial infarction and cerebrovascular disease often manifesting as stroke (Forbes and Cooper 2013). Common conditions coexisting with type 2 diabetes (i.e., hypertension and dyslipidemia) are independent risk factors for cardiovascular disease (American Diabetes Association 2012). Diabetes is independently associated with a twofold to fourfold increase in the risk of cardiovascular disease (Stamler et al. 1993; Kannel and McGee 1979). Furthermore, diabetes is considered to be a cardiovascular disease risk equivalent; i.e., patients with diabetes without a history of myocardial infarction have a risk of myocardial infarction that is similar to that among nondiabetic subjects who have had a prior myocardial infarction (Haffner et al. 1988).

## Microvascular Complications

Microvascular complications of diabetes include nephropathy, retinopathy, and neuropathy. *Diabetic retinopathy* is a highly specific microvascular complication of diabetes mellitus, and its prevalence is strongly related to the duration of diabetes (American Diabetes Association 2012). *Diabetic nephropathy* occurs in 20–40 % of the patients with diabetes and is the leading cause of *end-stage renal disease (ESRD*) worldwide (American Diabetes Association 2012). Although the risk of renal complications was initially thought to be lower in patients with type 2 diabetes than in those with type 1 diabetes (Fabre et al. 1982), to date, there is evidence that the risk of nephropathy is similar among patients with type 1 and 2 diabetes (Hasslacher et al. 1989; Ritz and Orth 1999).

Worldwide, the burden of diabetic nephropathy is enormous. Diabetes is estimated to increase the risk of ESRD by approximately 12-fold (Adler et al. 2003; Brancati et al. 1997). A disproportionately large percentage of patients with ESRD have diabetes, and, at this moment, diabetic nephropathy and hypertension, which often co-occur, are the major causes for ESRD in the United States (Fig. 1; Adler et al. 2003; Collins et al. 2014; Reutens 2013).

Furthermore, patients with diabetic nephropathy are at an increased risk for cardiovascular morbidity and mortality. Using data from over 5,000 subjects with type 2 diabetes participating in the United Kingdom Prospective Diabetes Study (UKPDS), it was estimated that each year 2.3 % of the subjects with macroalbuminuria progress to either elevated plasma creatinine ($\geq$175 μmol/L) or renal replacement therapy (Adler et al. 2003). In this latter study, it was also shown that the risk of all-cause mortality (annual death rate 4.6 %) exceeded the risk for progression to elevated plasma creatinine or renal replacement therapy (Adler et al. 2003). Analogous to the fact that, diabetes can be considered a cardiovascular disease equivalent, Tonelli et al. demonstrated that the incidence of myocardial infarction was similar in subjects with diabetes without CKD and subjects without diabetes but with CKD. This suggests that CKD is also a cardiovascular disease equivalent (Tonelli et al. 2012). In subjects with both diabetes and CKD, the risk of myocardial infarction and all-cause mortality was even higher (Tonelli et al. 2012).

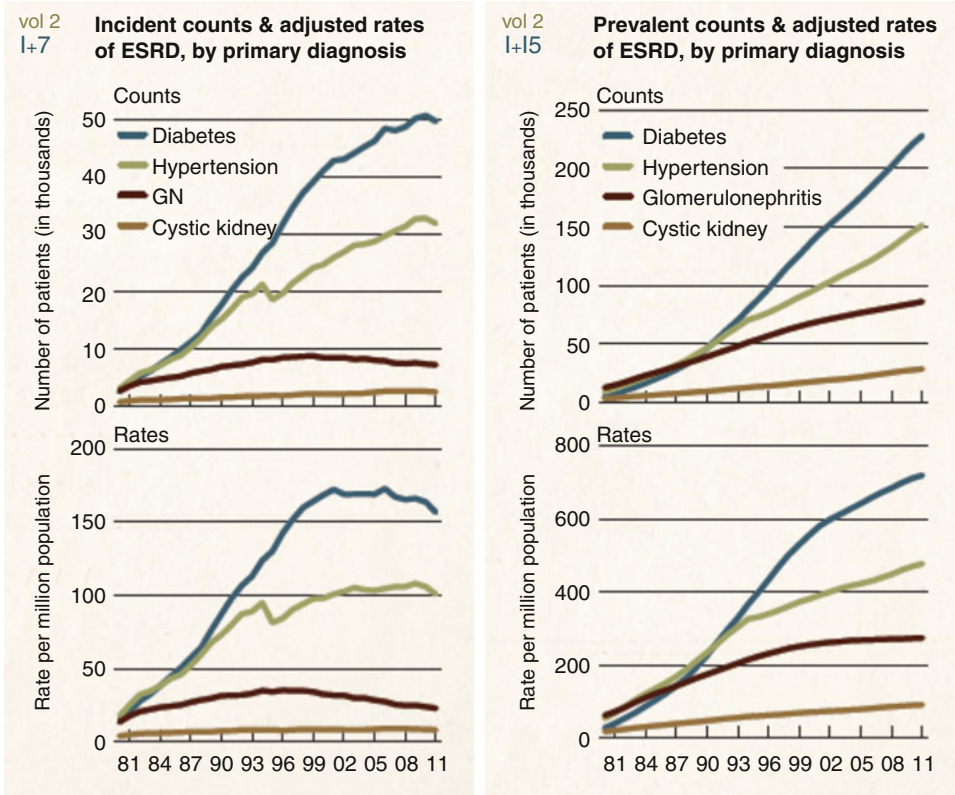


**Fig. 1** Incidence and prevalence of ESRD by primary diagnosis (Data adapted from the US Renal Data System 2013)

## Histopathology of Diabetic Nephropathy

Characteristic glomerular changes of diabetic nephropathy include thickening of the glomerular basement membrane (GBM), mesangial expansion, and podocyte injury. These classic glomerular changes are shown in Fig. 2 (adapted from Jefferson et al. (2008)).

In 2010, a pathologic classification of diabetic nephropathy was proposed by the Research Committee of the Renal Pathology Society. This publication of Tervaert et al. (2010) forms the basis of this chapter's section on the histopathology of diabetic nephropathy. Since type 1 and type 2 diabetic nephropathies share similar histologic characteristics as well as structural-functional relationships, one common classification is used for both type 1 and 2 diabetes (Tervaert et al. 2010; White and Bilous 2000). Figure 3, adapted from Tervaert et al. (2010), depicts the individual steps relevant for histopathological staging of diabetic nephropathy.

## Histologic Characteristics

### Glomerular Lesions

As early as 1–2 years after the onset of diabetes, *glomerular basement membrane (GBM) thickening*, the first hallmark of diabetic nephropathy, occurs and increases with the duration of the disease (Tsilibary 2003; Perrin et al. 2006). GBM thickening is the result of extracellular matrix accumulation with increased deposition of normal extracellular matrix components (collagen IV and VI, laminin, and fibronectin), whereas the expression of heparan sulfate proteoglycans and the extent of sulfation decrease (Raats et al. 2000). Cutoff levels for GBM thickening by direct measurement of membrane thickness with electron

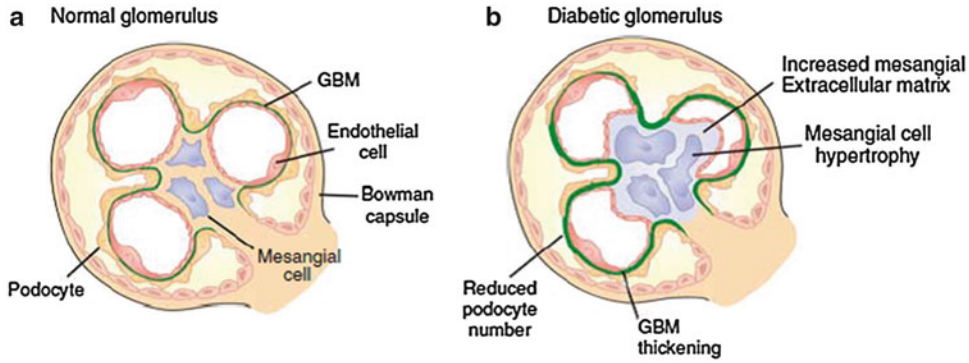


**Fig. 2** Characteristic glomerular changes of diabetic nephropathy. (**a**) Normal glomerulus. Cells of the glomerular tuft (mesangial cells, endothelial cells, and podocytes) and extracapillary glomerulus (parietal epithelial cells) are shown, along with the GBM. (**b**) Diabetic kidney. In the diabetic kidney, characteristic glomerular changes include thickening of GBM and mesangial expansion (due to increased mesangial matrix and increased mesangial cell size due to hypertrophy). The filtration surface is reduced due to mesangial expansion, leading to reduced glomerular filtration rate. Podocytes undergo several changes, including a reduction in cell number as illustrated (Figure adapted from Jefferson et al. (2008))

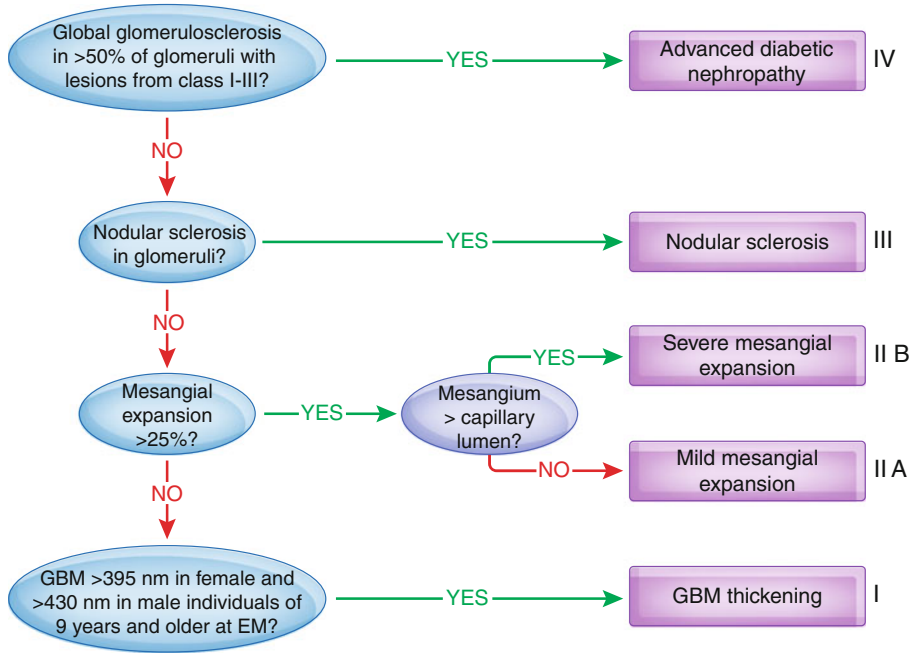


**Fig. 3** Flow chart for classification of diabetic nephropathy (Figure adapted from Tervaert et al. (2010))

microscopy (EM) are >430 nm in males of 9 years and older and >395 nm in females of the same age group (Tervaert et al. 2010; Haas 2009). Isolated GBM thickening has been described as a prediabetic lesion in patients with proteinuria who subsequently developed diabetes mellitus (Mac-Moune et al. 2004).

The second hallmark of diabetic nephropathy is expansion of cellular and matrix components in the mesangium (Adler 1994). In the current classification scheme (Tervaert et al. 2010), no distinction is made between mesangial hypercellularity, matrix expansion, and "mesangiosclerosis." *Mesangial expansion* is

defined as an increase in extracellular material in the mesangium such that the width of the interspace exceeds two mesangial cell nuclei in at least two glomerular lobules and >25 % of the observed mesangium is affected (Tervaert et al. 2010). If the expanded mesangial area is larger than the mean area of a capillary lumen, the mesangial expansion is classified as severe.

The presence of at least one *Kimmelstiel-Wilson lesion* (nodular sclerosis) represents more advanced diabetic nephropathy (Kimmelstiel and Wilson 1936). A Kimmelstiel-Wilson lesion is a focal, lobular, round to oval mesangial lesion with an acellular, hyaline/matrix core, rounded peripherally by sparse, crescent-shaped mesangial nuclei (Tervaert et al. 2010; Stout et al. 1993). It is postulated that microvascular injury due to mesangiolysis (i.e., lytic changes in the mesangial area) and detachment of endothelial cells from the GBM precedes the formation of Kimmelstiel-Wilson lesions (Nishi et al. 2000). Clearly, a Kimmelstiel-Wilson lesion destroys the normal structure of the glomerulus. When more than 50 % of the glomeruli show global glomerulosclerosis, advanced diabetic nephropathy is present (Fig. 4, Table 2; both adapted from Tervaert et al. (2010)).

### Tubular and Vascular Lesions

Concomitant *tubular* basement membrane thickening is present from the stage of mesangial expansion onwards (Tervaert et al. 2010). Generally, interstitial fibrosis and tubular atrophy follow glomerular changes. Also, inflammatory interstitial infiltrates consisting of T lymphocytes and macrophages are often observed (Tervaert et al. 2010; Bohle et al. 1991).

"Insudative lesions," if present, may help diagnosing diabetic nephropathy. Insudative lesions refer to material accumulated within (therefore, *in*sudative rather than *ex*udative) the walls of the capillaries or arterioles (Stout et al. 1994). These lesions consist of accumulations of plasma proteins and lipids. Hyalinosis of the *efferent* arterioles is considered relatively specific for diabetic nephropathy (Tervaert et al. 2010; Stout et al. 1994). Arteriolar hyalinosis of the *afferent* arteriole occurs, apart from diabetes, in many other conditions, e.g., hypertension, cyclosporine nephropathy, and atherosclerosis. If insudative lesions are present in Bowman's capsule, these lesions are called capsular drop lesions, which are prevalent in more advanced diabetic nephropathy (Tervaert et al. 2010; Bloodworth 1978). Glomerular capillary hyalinosis is a nonspecific lesion that can also be found in other conditions, e.g., focal glomerulosclerosis.

## Structural-Functional Associations

In diabetic nephropathy, there appears to be a close relationship between the clinical manifestations of diabetic nephropathy and structural renal changes (White and Bilous 2000; Fioretto and Mauer 2007).

For example, GBM thickening is related to long-term blood glucose control and urinary albumin excretion (White and Bilous 2000; Fox et al. 1977), and the loss of negatively charged proteoglycans in the GBM correlates with the degree of proteinuria (Roscioni et al. 2014b). Yet, loss of negative charges has recently been challenged as the main cause of albuminuria in diabetic nephropathy. Podocytopathy (i.e., decreased number and/or density of podocytes as a result of podocyte-apoptosis and detachment) and loss of nephrin in the slit diaphragm are suggested to be pivotal events, as is the role of abnormal tubular handling of ultrafiltrated protein (Ziyadeh and Wolf 2008).

When the mesangium expands, glomerular capillaries are distorted and compressed with ensuing decrease in capillary filtration surface. As a result, mesangial volume inversely relates to glomerular filtration rate (GFR). Both mesangial and interstitial expansion correlate with decreased renal function (White and Bilous 2000). The occurrence of Kimmelstiel-Wilson lesions heralds the transition to more advanced diabetic nephropathy and is reflected by decreased renal function and a poor prognosis (Tervaert et al. 2010).

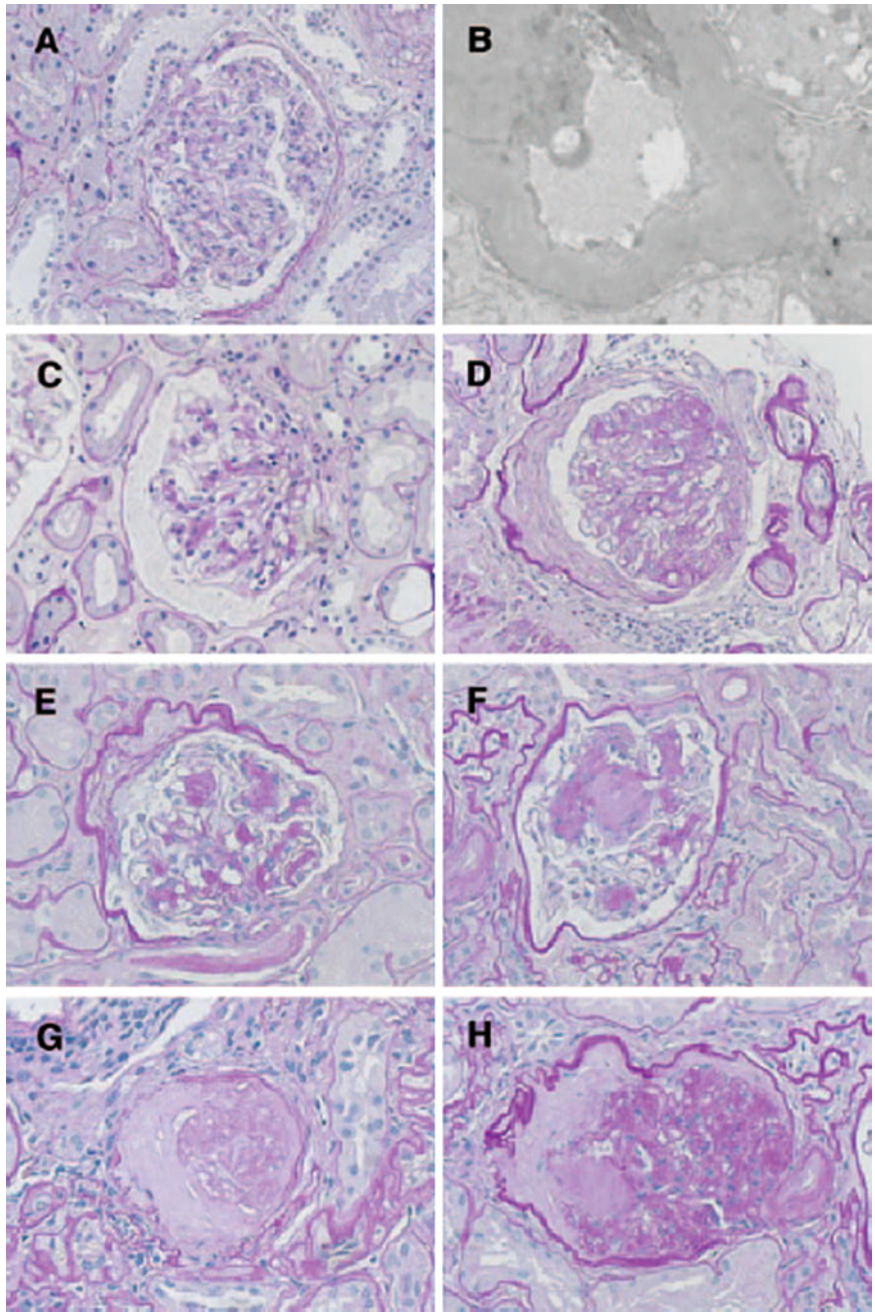


**Fig. 4** Representative examples of morphologic lesions in diabetic nephropathy. (**a**) Glomerulus showing only mild ischemic changes, with splitting of Bowman's capsule. No clear mesangial alternation. (**b**) EM of this glomerulus: the mean width of the GBM was 671 nm. EM provides the evidence for classifying the biopsy with only mild light microscopic changes into class I. (**c**, **d**) Class II glomeruli with mild and moderate mesangial expansion, respectively. In panel **c**, the mesangial expansion does not exceed the mean area of a capillary lumen (IIa), whereas in paned **d** it does (IIb). (**e**, **f**) In panel **f** is a class III Kimmelstiel-Wilson lesion. The lesion in panel **e** is not a convincing Kimmelstiel-Wilson lesion; therefore (on the basis of findings in this glomerulus), the finding is consistent with class IIb. For the purpose of the classification, at least one convincing Kimmelstiel-Wilson lesion (as in panel **f**) needs to be present. In panel **h**, signs of class IV diabetic nephropathy consist of hyalinosis of the glomerular

**Table 2** Glomerular classification of diabetic nephropathy (Adapted from Tervaert et al. (2010))

| Class | Description | Inclusion criteria |
|---|---|---|
| I | Mild or nonspecific LM changes and EM-proven GBM thickening | Biopsy does not meet any of the criteria mentioned below for class II, III, or IV |
| | | GBM >395 nm in female and >430 nm in male individuals 9 years of age and older[a] |
| IIa | Mild mesangial expansion | Biopsy does not meet criteria for class III or IV |
| | | Mild mesangial expansion in >25 % of the observed mesangium |
| IIb | Severe mesangial expansion | Biopsy does not meet criteria for class III or IV |
| | | Severe mesangial expansion in >25 % of the observed mesangium |
| III | Nodular sclerosis (Kimmelstiel-Wilson lesion) | Biopsy does not meet criteria for class IV |
| | | At least one convincing Kimmelstiel-Wilson lesion |
| IV | Advanced diabetic glomerulosclerosis | Global glomerular sclerosis in >50 % of glomeruli |
| | | Lesions from classes I through III |

*LM*, light microscopy
[a]Based on direct measurement of GBM width by EM, these individual cutoff levels may be considered indicative when other GBM measurements are used

## Clinical Course of Diabetic Nephropathy

The clinical course of the development and progression of diabetic nephropathy is depicted in Fig. 5. The clinical manifestations of diabetic nephropathy are similar in both type 1 and type 2 diabetes (Fioretto and Mauer 2007). Based on urinary albumin excretion (UAE), diabetic nephropathy can be divided in three stages (i.e., normoalbuminuria, microalbuminuria, and macroalbuminuria (Table 3)). The term microalbuminuria is widely used to denote low-grade albuminuria (i.e., a UAE of 30–300 mg/day) and identifies those at risk for diabetic nephropathy and cardiovascular disease (Jefferson et al. 2008). However, it is now well recognized that even in the "submicroalbuminuric" range (i.e., a UAE of 2–30 mg/day), the risk of cardiovascular disease increases with the degree of UAE (Jefferson et al. 2008). Therefore, UAE should rather be considered as a continuous variable than using specific cutoff values. Nonetheless, we use the three stages of diabetic nephropathy according to UAE cutoff values to describe the clinical course of diabetic nephropathy.

### Normoalbuminuria

Hemodynamic changes have been reported early in diabetes and are characterized by an increase in kidney size (i.e., hypertrophy) and glomerular filtration rate (i.e., *glomerular hyperfiltration*). The prevalence of glomerular hyperfiltration in type 1 diabetes varies from 25 % to 75 % (Jerums et al. 2010). In patients with type 2 diabetes, the prevalence of glomerular hyperfiltration is lower (i.e., ranging between 0 % and >40 %) (Jerums et al. 2010; Vora et al. 1992). Glomerular hyperfiltration was found to be closely related to the degree of hyperglycemia and can be reversed

**Fig. 4** (continued) vascular pole and a remnant of a Kimmelstiel-Wilson lesion on the opposite site of the pole. Panel **g** is an example of glomerulosclerosis that does not reveal its cause (glomerulus from the same biopsy as panel **h**). For the purpose of the classification, signs of diabetic nephropathy should be histopathologically or clinically present to classify a biopsy with global glomerulosclerosis in >50 % of glomeruli as class IV (Figure adapted from Tervaert et al. (2010))

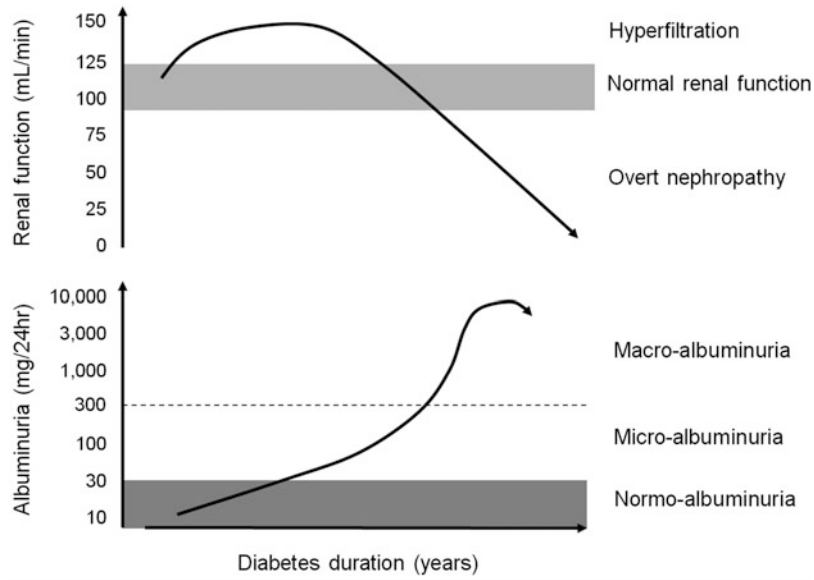


**Fig. 5** The clinical course of the development and progression of diabetic nephropathy

**Table 3** Stages of diabetic nephropathy based on urinary albumin excretion

| | Urinary albumin excretion | Albumin to creatinine ratio |
|---|---|---|
| Stage | (mg/24 h) | (mg/g) |
| Normoalbuminuria | <30 | <30 |
| Microalbuminuria | 30–300 | 30–300 |
| Macroalbuminuria | >300 | >300 |

by intensified glycemic control in both type 1 and type 2 diabetes (Jerums et al. 2010; Wiseman et al. 1985).

The mechanisms mediating diabetes-induced glomerular hyperfiltration have not yet been fully elucidated, but potential glomerular and tubular theories have been proposed. One of the hypotheses for hyperfiltration in diabetes states that increased glomerular capillary pressures and flows are implicated in the development and progression of diabetic nephropathy (Hostetter et al. 1982). In line with this hypothesis, a study of Zatz et al. showed that hemodynamic rather than metabolic factors mediate diabetic glomerulopathy in rats with streptozotocin-induced diabetes (Zatz et al. 1985). The most commonly accepted hypothesis for diabetic hyperfiltration, "the tubular hypothesis of glomerular hyperfiltration," however, states that the increased glomerular filtration rate (GFR) is a result of an increased proximal tubular reabsorption of glucose and sodium by the sodium-glucose cotransporters, which subsequently leads to a reduced load of sodium and chloride to the macula densa and inactivation of the *tubuloglomerular feedback (TGF) mechanism* (Persson et al. 2010). Suppression of the TGF mechanism results in a reduced afferent arteriolar vasoconstriction and a subsequent increase in GFR (Persson et al. 2010). However, diabetes-induced hyperfiltration has also been shown to occur in adenosine $A_1$-receptor knockout mice that lack the TGF mechanism (Jerums et al. 2010; Sallstrom et al. 2007).

The presence of glomerular hyperfiltration has been suggested to be a risk factor for development of diabetic nephropathy (Mogensen et al. 1990). Several longitudinal studies demonstrated an association between glomerular hyperfiltration and the risk of development and progression of diabetic nephropathy (Mogensen 1986; Chiarelli et al. 1995; Amin et al. 2005). However, conflicting results have also been published (Jerums et al. 2010; Thomas et al. 2012; Chatzikyrkou and Haller 2012). The assessment of the relationship of hyperfiltration with progression of nephropathy is subject to several methodological difficulties

(Jerums et al. 2010; Chatzikyrkou and Haller 2012). The first methodological difficulty relates to the follow-up period of the studies (Jerums et al. 2010). As diabetic nephropathy progresses over more than 10–20 years, a long follow-up period is required to study the consequences of glomerular hyperfiltration on progression of diabetic nephropathy. An additional methodological problem relates to the shortcomings of current creatinine-based methods to estimate GFR at higher levels of GFR at which the creatinine-based methods underestimate the measured GFR (Jerums et al. 2010; Chatzikyrkou and Haller 2012). A study performed by Gaspari et al. demonstrated that actual measured GFR was underestimated by ~20–50 mL/min/1.73 $m^2$ when estimating equations were used to assess GFR in hyperfiltering patients with type 2 diabetes (Gaspari et al. 2013). In a large proportion of the hyperfiltering patients with type 2 diabetes, glomerular hyperfiltration was missed by estimating equations, irrespective of which equation was used (Gaspari et al. 2013).

## Microalbuminuria

In 1969, the presence of *microalbuminuria* (i.e., a UAE of 30–300 mg/24 h) was first described in subjects with diabetes (Keen et al. 1969; Parving et al. 2006). The equivalent definition of microalbuminuria based on urinary albumin to creatinine ratio (ACR) is 2.5–25 mg/mmol (25–250 mg/g) for men and 3.5–35 mg/mmol (35–350 mg/g) for women (Jerums et al. 2009).

Although approximately 20 % (180 L) of renal plasma flow is filtered at the glomerulus each day, only small amounts of proteins and albumin appear in urine of healthy individuals (Jefferson et al. 2008). Proteins filtered at the glomerulus are taken up by, and degraded in, proximal tubular cells and are subsequently reabsorbed into peritubular capillaries (Jefferson et al. 2008). The relative impermeability of the glomerular capillary membrane to macromolecules such as albumin is due to the size-selective and charge-selective properties of the glomerular capillary membrane and hemodynamic forces operating across the capillary wall (Jefferson et al. 2008; Rennke and Denker 2010). It has been estimated that the effective glomerular pore radius for spherical molecules is about 42 angstroms (Å), whereas albumin has a molecular radius of 36 Å (Rennke and Denker 2010). Furthermore, the glomerular capillary wall contains negatively charged moieties, which restricts the filtration of anionic macromolecules such as albumin (Rennke and Denker 2010). Anionic charges have been demonstrated in all of the filtration barrier structures, i.e., the endothelial cell glycocalyx, the glomerular basement membrane, and the podocyte glycocalyx (Jeansson and Haraldsson 2006). The glycocalyx is a thin layer of proteoglycans with their associated glycosaminoglycans that covers the outer endothelial layer and its fenestrae in a gel-like diaphragm and excludes (charged) macromolecules from the ultrafiltrate (Roscioni et al. 2014b).

In diabetic nephropathy, albuminuria is a consequence of defects in the glomerular filtration barrier, but abnormalities in tubular reabsorption of albumin may also contribute (Jefferson et al. 2008). The exact mechanism of the increase in glomerular permeability remains unclear. Increased intra-glomerular pressure (Zatz et al. 1985), damage to the endothelial glycocalyx (Singh et al. 2011; Nieuwdorp et al. 2006), loss of glomerular charge selectivity (Deckert et al. 1988; Deckert et al. 1993), altered glomerular size selectivity (Nakamura and Myers 1988), and injury to podocytes (Jefferson et al. 2008; Wolf and Ziyadeh 2007; Li et al. 2007) have been observed in diabetic nephropathy and have been proposed as potential mechanisms for increased glomerular permeability (Fig. 6; adapted from Jefferson et al. (2008)).

Epidemiological studies have indicated that microalbuminuria is associated with clinical risk factors such as hyperglycemia, systolic and diastolic blood pressure, smoking, and estimated GFR (Parving et al. 2006; Afghahi et al. 2011). Moreover, the presence of microalbuminuria was found to be an important independent risk factor for the development of both diabetic nephropathy and cardiovascular disease (CVD) (Satchell and Tooke 2008; Rossing et al. 1996; Dinneen and Gerstein 1997). The relationship between

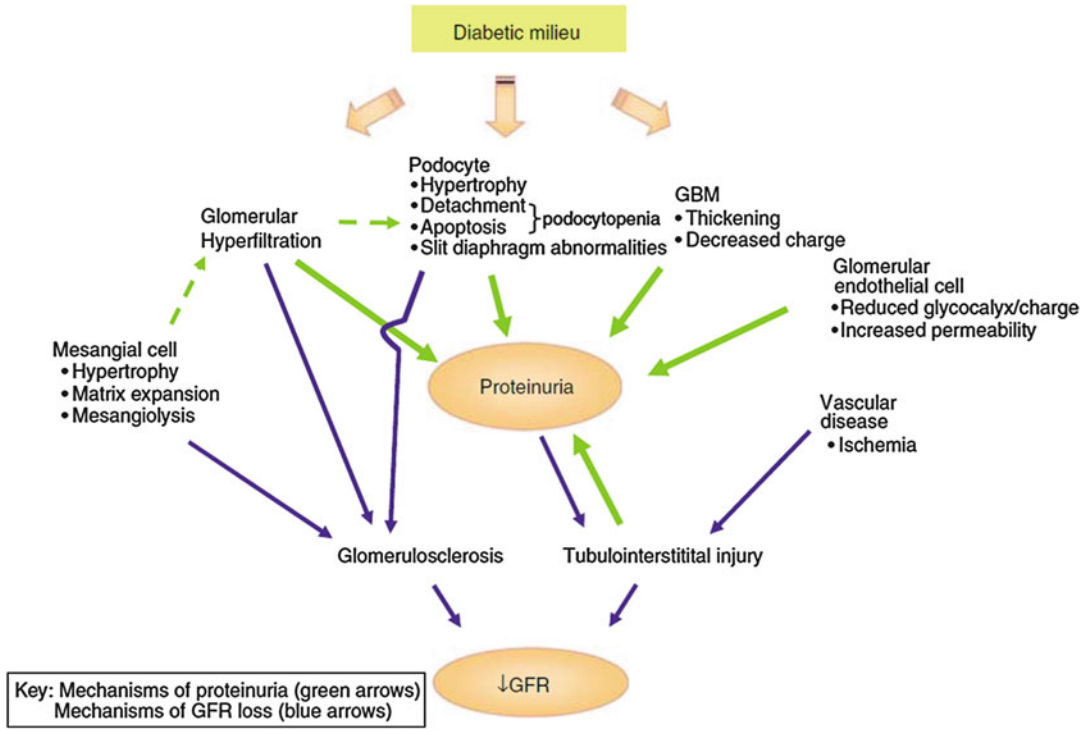


**Fig. 6** Proposed scheme unifying the mechanisms of proteinuria and decrease in GFR in diabetic nephropathy. This scheme summarizes events leading to albuminuria/proteinuria (*green arrows*) and reduced GFR (*purple arrows*) in patients with diabetic nephropathy. The diabetic milieu has effects on all cell types within the kidney (represented by the *thick arrows*), and these contribute either primarily or secondarily to the development of albuminuria/proteinuria and reduced GFR. At the level of the glomerulus, both hemodynamic effects and injury to the individual components of the glomerular filtration barrier (podocyte, GBM, and glomerular endothelial cell) primarily lead to proteinuria (*green arrows)*. In addition, tubulointerstitial injury may diminish tubular protein reuptake. Mesangial cell injury likely contributes secondarily to proteinuria by (i) mesangial expansion causing a loss of glomerular filtration surface area leading to glomerular hyperfiltration (*dashed green arrows*) or (ii) by mesangiolysis leading to structural changes in the capillary loops. Proteinuria itself may result in a decrease in GFR by causing tubulointerstitial injury (Figure adapted from Jefferson et al. (2008))

microalbuminuria and vascular disease suggests a common causality, and unifying mechanisms such as generalized endothelial dysfunction and inflammation have been proposed (Satchell and Tooke 2008; Stehouwer and Smulders 2006). Indeed, several studies have reported associations of microalbuminuria with endothelial dysfunction and chronic low-grade inflammation in type 1 and type 2 diabetes (Stehouwer et al. 2004; Persson et al. 2008a; Schalkwijk et al. 1999). Furthermore, Salmon et al. reported that loss of endothelial glycocalyx links albuminuria to vascular dysfunction (Salmon and Satchell 2012), supporting the notion that microalbuminuria is not only a marker of renal damage but also a marker of generalized endothelial dysfunction (Roscioni et al. 2014a; Deckert et al. 1989).

Microalbuminuria was found to be closely related to the development of diabetic nephropathy. In the United Kingdom Prospective Diabetes Study (UKPDS), it was reported that the annual rate of patients with type 2 diabetes and persistent microalbuminuria that progressed to diabetic nephropathy was 2.8 % (Adler et al. 2003). However, increasing evidence demonstrated that microalbuminuria also might revert to normoalbuminuria in both type 1 and type 2 diabetes (Perkins et al. 2003; Gaede et al. 2004; Araki et al. 2005). Factors associated with remission of microalbuminuria in diabetes included

initiation of antihypertensive therapy, a decrease in systolic blood pressure, a decrease in levels of cholesterol, triglycerides, and $HbA_{1c}$ (Perkins et al. 2003; Gaede et al. 2004). Importantly, remission of microalbuminuria, whether spontaneous or treatment-induced, has been associated with a decreased rate of progression toward diabetic nephropathy, a decreased rate of renal function decline, and a decreased risk of cardiovascular morbidity and mortality (Jerums et al. 2009; Araki et al. 2007; Zandbergen et al. 2007).

### Macroalbuminuria

Clinically, *diabetic nephropathy* is characterized by the development of persistent *macroalbuminuria* (i.e., UAE >300 mg/24 h) or proteinuria (i.e., urinary protein excretion >0.5 g/24 h), blood pressure elevation, and a decline in glomerular filtration rate. Studies investigating the progression of diabetic nephropathy have demonstrated a continuous, often linear, but highly variable, rate of decline in GFR in both subjects with type 1 and type 2 diabetes and nephropathy (Parving 2001; Gall et al. 1993; Ritz and Stefanski 1996; Hovind et al. 2001).

Several risk factors for progression of diabetic nephropathy have been identified. A close inverse correlation of the degree of glomerular and tubulointerstitial lesions with GFR and decline in GFR was found in morphologic studies in both type 1 and type 2 diabetes (Najafian and Mauer 2009, 2012; Christensen et al. 2001). Blood pressure was found to be associated with renal function decline in patients with type 1 and type 2 diabetes (Hovind et al. 2001; Taft et al. 1994; Yokoyama et al. 1997; Bakris et al. 2003; Rossing et al. 1993), which suggests that elevated blood pressure accelerates the progression of diabetic nephropathy. Furthermore, it has been suggested that albuminuria itself contributes to renal damage and, consequently, progressive loss of renal function (Taft et al. 1994; Yokoyama et al. 1997; Rossing et al. 1993; Nelson et al. 1996; Remuzzi and Bertani 1990). Once albumin is filtered at the glomerulus, it is taken up by and degraded in proximal tubular cells. However, an increased albumin exposure in the tubular compartment could trigger a number of toxic effects and inflammatory responses (Fig. 7; Roscioni et al. 2014a). In vitro studies have shown that increased albumin exposure in tubular cells exerts cytotoxic effects on proximal and distal tubular cells by activating a range of intracellular signaling pathways (Morigi et al. 2002; Lee et al. 2003; Dixon and Brunskill 1999; Drumm et al. 2002; Reich et al. 2005; Wang et al. 1999), which induce the release of inflammatory (Wang et al. 1999; Zoja et al. 1998; Wang et al. 1997), vasoactive (Vlachojannis et al. 2002; Whaley-Connell et al. 2007; Zoja et al. 1995), and fibrotic substances (Diwakar et al. 2007; Goumenos et al. 2002; Stephan et al. 2004; Wohlfarth et al. 2003), causing interstitial damage and ultimately leading to irreversible renal function loss (Roscioni et al. 2014b). Moreover, increased albumin exposure in tubular cells may also cause cellular apoptosis (Tejera et al. 2004; Koral and Erkan 2012), which results in decreased nephron functionality (Roscioni et al. 2014b).

Patients with diabetic nephropathy are at an increased risk for cardiovascular morbidity and mortality (Forbes and Cooper 2013; Parving 2001). In addition, despite available treatment strategies, the risk for progression to *ESRD* remains very high.

## Screening and Diagnosis

### Screening

Annual screening for patients with diabetes is widely recommended to detect the early onset of diabetic nephropathy and to reduce the risk or slow the progression of diabetic nephropathy (American Diabetes Association 2012; Farmer et al. 2014; KDOQI 2007). In patients with type 1 diabetes with a disease duration of ≥5 years and in all patients with type 2 diabetes, it is recommended to perform an annual test to assess urine albumin excretion (American Diabetes Association 2012; KDOQI 2007). Since the intraindividual variability in urinary albumin

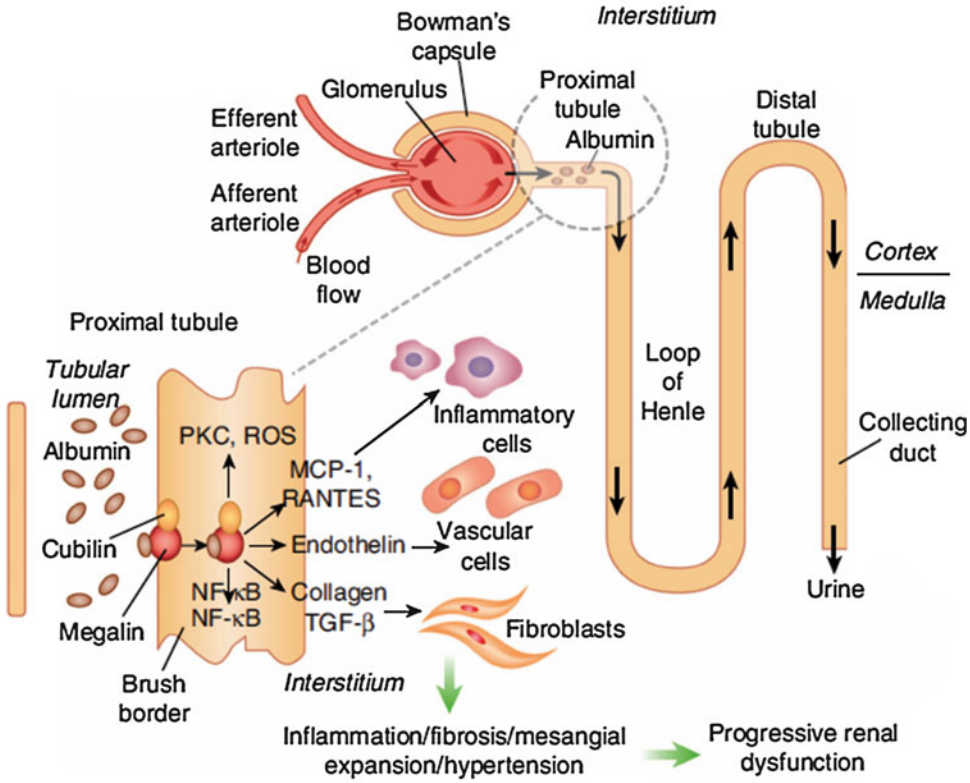


**Fig. 7** Pathophysiological mechanisms of albumin-induced progressive renal dysfunction. Once albumin has passed the glomerular barrier, it undergoes reuptake by the tubular cells because of the cubilin-megalin complex. Albumin triggers a cascade of pathogenic mechanisms leading to inflammation, fibrosis, mesangial expansion, and hypertension, which ultimately cause progressive renal dysfunction. These mechanisms encompass the activation of intracellular signaling pathways (e.g., extracellular signal-regulated kinase (*ERK*), nuclear factorkB (*NF-kB*), protein kinase C (*PKC*)) and release of inflammatory (monocyte chemotactic protein-1 (*MCP-1*), regulated on activation normal T cell expressed and secreted (*RANTES*)) vasoactive (reactive oxygen species (*ROS*), endothelin, and fibrotic (tumor growth factor-b (*TGF-b*), collagens) substances, leading to irreversible renal damage (Figure adapted from Roscioni et al. (2014b))

excretion is high (i.e., 20–50 %), the staging of albuminuria based on a single measurement of UAE or ACR results in an inadequate assessment. Therefore, it is recommended that the categorization of persistent albuminuria is based on at least three urine samples that are not taken in the presence of intercurrent illness or after strenuous exercise (American Diabetes Association 2012; Mogensen et al. 1995). In addition, it is recommended to measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate GFR and stage the level of CKD (Fig. 8), if present (American Diabetes Association 2012).

## Diagnosis

Attributing impaired renal function to diabetes typically requires either a renal biopsy (golden standard) or the presence of a constellation of clinical findings (Van Buren and Toto 2013a). Classic features of diabetic nephropathy are GBM thickening, mesangial expansion, and Kimmelstiel-Wilson lesions (nodular sclerosis) (Tervaert et al. 2010; Schwartz et al. 1998; Van Buren and Toto 2013a; Osterby et al. 1993). A renal biopsy may be deferred with the assumed diagnosis of diabetic nephropathy in case of macroalbuminuria in the presence of diabetic retinopathy and microalbuminuria in type 1 diabetes of at least

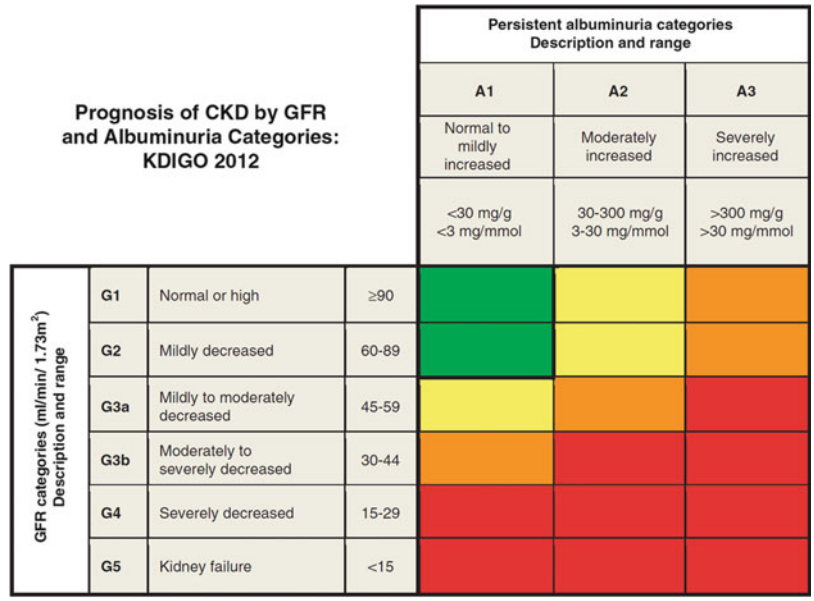


**Fig. 8** Stages of chronic kidney disease according to the KDIGO 2012 guidelines

10 years' duration (KDOQI 2007). It is important to note that the absence of diabetic retinopathy by no means rules out diabetic nephropathy. However, in such cases, when definite evidence for diabetic nephropathy is obligatory, renal biopsy should be considered. Other causes of kidney disease should be considered in the absence of diabetic retinopathy, low or rapidly decreasing GFR, rapidly increasing proteinuria or nephritic syndrome, refractory hypertension, presence of active urinary sediment, signs or symptoms of other systemic diseases, or >30 % reduction in GFR within 2–3 months after initiation of treatment with an ACE inhibitor or ARB (KDOQI 2007).

## Treatment Strategies

Several treatment strategies are available that have been demonstrated to reduce the risk of developing nephropathy and to slow the progression hereof. Early identification of patients at risk for diabetic nephropathy may allow optimization of preventive measures to reduce the incidence and progression of diabetic nephropathy (Fig. 9). Key treatment strategies include blood glucose control, blood pressure control, lipid-lowering therapy, and lifestyle interventions.

### Blood Glucose Control

Achieving optimal *blood glucose control* is essential to delay the onset and slow the progression of renal complications in both type 1 and type 2 diabetes. Early in the clinical course of diabetes, optimizing blood glucose control results in normalization of hyperfiltration (Jerums et al. 2010; Wiseman et al. 1985; Van Buren and Toto 2013a; Mogensen 1971). Improved glycemic control also reduces urinary albumin excretion (The Diabetes Control and Complications Trial Research Group 1993; The Diabetes Control and Complications (DCCT) Research Group 1995). Although intensified blood glucose control decreases GFR in the short term, it could preserve renal function over time (Van Buren and Toto 2013a; Feldt-Rasmussen et al. 1991).

In a meta-analysis performed by Wang et al., it was shown that long-term intensive blood glucose control significantly reduces the risk of progression of diabetic nephropathy (Wang et al. 1993). Intensive blood glucose control also effectively delayed the onset and progression of microvascular complications in subjects with type 1 diabetes included in the Diabetes Control and Complications Trial (DCCT) (The Diabetes Control and Complications Trial Research Group 1993) and

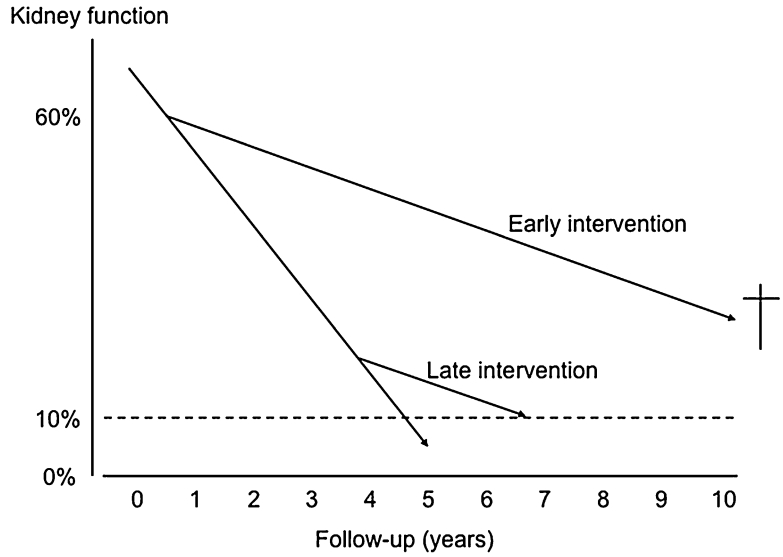


**Fig. 9** Effect of early and late intervention on kidney function decline

in subjects with type 2 diabetes included in the UKPDS trial (UK Prospective Diabetes Study (UKPDS) Group 1998). Tight glycemic control with a target $HbA_{1c}$ of <6.5 % (<47.5 mmol/mol) has also been shown to reduce the incidence and progression of nephropathy in the more recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial that was conducted in subjects with type 2 diabetes at cardiovascular risk (ADVANCE Collaborative Group et al. 2008).

The beneficial results of randomized controlled trials on tight blood glucose control and the consistent association of $HbA_{1c}$ with *microvascular complications* in both type 1 and type 2 diabetes have initiated trials that investigated whether targeting $HbA_{1c}$ levels <6 % would further reduce the progression of diabetes-related cardiovascular complications (Heerspink and de Zeeuw 2011). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial studied the effects of very intensive glycemic therapy (targeted at a $HbA_{1c}$ <6 % [<42.1 mmol/mol]) compared to standard therapy ($HbA_{1c}$ 7–7.9 % [53–62.8 mmol/mol]) in subjects with type 2 diabetes (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008). However, after a mean follow-up of 3.5 years, intensive treatment in the ACCORD trial was stopped because of increased overall mortality in the intensive therapy group (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008). At time of discontinuation, the use of very intensive glycemic control (targeted at an $HbA_{1c}$ <6 % [<42.1 mmol/mol]) did not significantly reduce major cardiovascular events compared with standard therapy (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008). Although the incidence of micro- and macroalbuminuria was lower on intensive therapy, there was no significant effect of intensive therapy on advanced measures of microvascular complications (Ismail-Beigi et al. 2010). Proposed explanations for the unexpected higher mortality rates in the intensive treatment group of the ACCORD trial include drug-induced increases in body weight and fluid retention (Heerspink and de Zeeuw 2011; Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008). Furthermore, hypoglycemic episodes occurred more frequently during very intensive blood glucose control (Action to Control Cardiovascular Risk in Diabetes Study Group et al. 2008). In both outpatient diabetes-related cohorts and trials of intensive glycemic control, severe hypoglycemia was found to be associated with an increased risk for all-cause mortality (Majumdar et al. 2013; Zhao et al. 2012; UK Hypoglycaemia Study Group 2007).

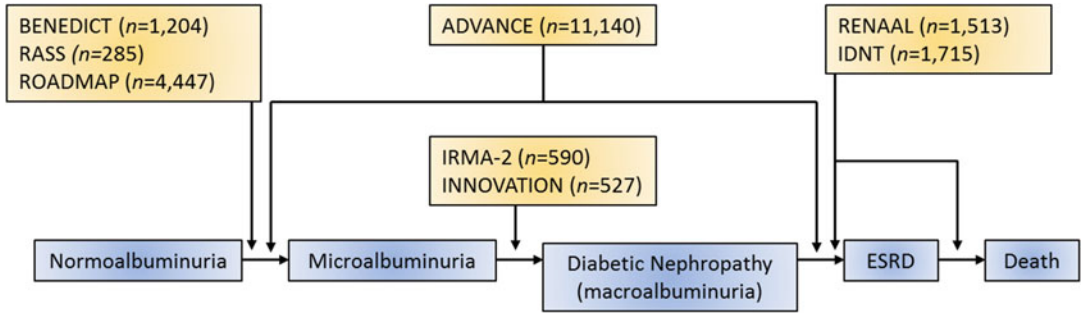


**Fig. 10** Randomized controlled trials that have investigated the effects of interventions in the RAAS at various stages of progression of diabetic nephropathy (Figure adapted from Roscioni et al. (2014a))

In conclusion, achieving optimal glucose is essential to delay the progression of renal complications in diabetes. Tight glycemic control was found to reduce the risk of microvascular complications. Very tight glycemic control, however, targeted to a $HbA_{1c}$ level <6 % increases the risk of hypoglycemia which in turn increases risk of cardiovascular events and mortality.

## Blood Pressure Control

*Hypertension* and diabetes often co-occur, and the pathogenesis of hypertension in patients with diabetes and diabetic nephropathy is complex (Van Buren and Toto 2013a). Yet, it has been established that lowering blood pressure is one of the key aspects in the management of diabetic nephropathy (Van Buren and Toto 2013a).

### Conventional Antihypertensive Therapy

Several studies have shown that blood pressure lowering with the use of conventional antihypertensive agents (e.g., β-blockers, thiazide, and loop diuretics) resulted in a reduction in albuminuria and a decrease in the rate of renal function decline in patients with type 1 diabetes and nephropathy (Parving et al. 1983, 1985, 1987). Thus, there is evidence that conventional blood pressure-lowering therapy using conventional antihypertensive agents decelerates both the development of diabetic nephropathy and the progression of diabetic nephropathy (Van Buren and Toto 2013b).

### Interventions in the Renin-Angiotensin-Aldosterone-System (RAAS)

Monotherapy with either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is currently recommended as first-line therapy for patients with diabetic nephropathy (American Diabetes Association 2012; Van Buren and Toto 2013a). Diuretics, β-blockers, and calcium channel blockers should be used as addition to therapy with *ACEi* or *ARBs* to further lower blood pressure, if necessary, or as alternate therapy when RAAS inhibitors are not tolerated (American Diabetes Association 2012).

The effects of interventions in the RAAS at different stages of diabetic nephropathy have been investigated in various trials (Fig. 10; adapted from Roscioni et al. (2014a)). First, RAAS inhibition has been shown to delay the risk of developing microalbuminuria in hypertensive patients with diabetes (Roscioni et al. 2014a). The use of ACE inhibitors decreased the incidence of microalbuminuria in patients with type 2 diabetes and hypertension, but with normo*albuminuria*, participating in the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) (Ruggenenti et al. 2004). The use of ARBs, however, did not prevent the development of microalbuminuria in mainly normo*tensive* patients with diabetes included in analysis of the Diabetic Retinopathy Candesartan Trials-Renal Study (DIRECT-Renal) (Bilous et al. 2009). The use of ACEi or ARBs did also not reduce the risk of microalbuminuria in normo*tensive* subjects

with type 1 diabetes included in the renin-angiotensin system study (RASS) (Mauer et al. 2009). Results of the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study showed that the use of the ARB olmesartan delayed the onset of microalbuminuria in normo*albuminuric* patients with type 2 diabetes (Haller et al. 2011). Mean baseline systolic blood pressure in subjects participating in the ROADMAP trial was higher (i.e., 136 ± 15 mmHg) than in the DIRECT-Renal and RASS studies (i.e., 118 ± 10 and 120 ± 11 mmHg, respectively). The cumulative findings of the BENEDICT, DIRECT-Renal, RASS, and ROADMAP studies suggest that RAAS inhibition reduces the incidence of microalbuminuria in hypertensive patients with type 2 diabetes, but not in patients with diabetes without significant other comorbidities (Van Buren and Toto 2013a).

In patients with microalbuminuria, the use of RAAS inhibitors has been reported to delay the progression from micro- to macroalbuminuria (Laffel et al. 1995). The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Trial (IRMA-2) (Parving et al. 2001) and Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) (Makino et al. 2007) trials both showed that the use of ARBs significantly reduced the risk for progression of microalbuminuria to overt diabetic nephropathy (i.e., macroalbuminuria) (Parving et al. 2001; Lewis et al. 2001). This effect appeared to be independent of the blood pressure-lowering capacity of these agents.

Finally, in patients with overt diabetic nephropathy (i.e., macroalbuminuria), the use of ACEi and ARBs has been shown to slow the progression of diabetic nephropathy to ESRD. This has been demonstrated in both patients with type 1 and type 2 diabetes. In patients with type 1 diabetes and nephropathy, it has been shown that captopril delayed the progression of diabetic nephropathy to ESRD (Lewis et al. 1993). In type 2 diabetes, ARBs have been shown to be effective in delaying the progression from diabetic nephropathy to ESRD in two multinational large-scale prospective trials (i.e., the Reduction in Endpoints in Non-insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan [RENAAL] and the Irbesartan in Diabetic Nephropathy Trial [IDNT]) (Lewis et al. 2001; Brenner et al. 2001). Post hoc analyses of the RENAAL and IDNT trials showed that most of the long-term renal and cardioprotective effects of ARBs are explained by the ARB-induced reduction in albuminuria (Atkins et al. 2005; de Zeeuw et al. 2004).

Despite the promising results from interventions in the RAAS system at various stages of diabetic nephropathy, the absolute risk for ESRD remains extremely high (Fig. 11; adapted from Heerspink and de Zeeuw (2011)). When one compares the risk of ESRD or death with the risk of death of all treated cancers, it becomes clear that patients with diabetic nephropathy carry an enormous risk for mortality which exceeds the risk of mortality in cancer (Fig. 11; Heerspink and de Zeeuw 2011).

## Dual RAAS Blockade: ACEi Plus ARB

As diabetic nephropathy still progresses in many patients and the risk of ESRD remains extremely high despite treatment with RAAS inhibitors, there is a need for alternatives that might optimize blockade of the RAAS system. Since ACEi and ARBs have complementary effects on angiotensin II inhibition, combination of an ACEi with an ARB has been suggested to improve the renoprotective effects of monotherapy with an ACEi or ARB (Roscioni et al. 2014a).

Several studies have investigated the effects of dual RAAS blockade with an ACEi and an ARB. A meta-analysis of Kunz et al., investigating the effects of the combination of ACEi and ARBs on proteinuria in patients with nephropathy, reported an additional reduction in albuminuria of concomitant therapy with an ACEi and ARB compared with monotherapy (Kunz et al. 2008). Unfortunately, safety and long-term outcomes were not assessed in the included studies, which hinder the applicability of the findings of this study to clinical practice (Kunz et al. 2008). The large-scale Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) was the first study that

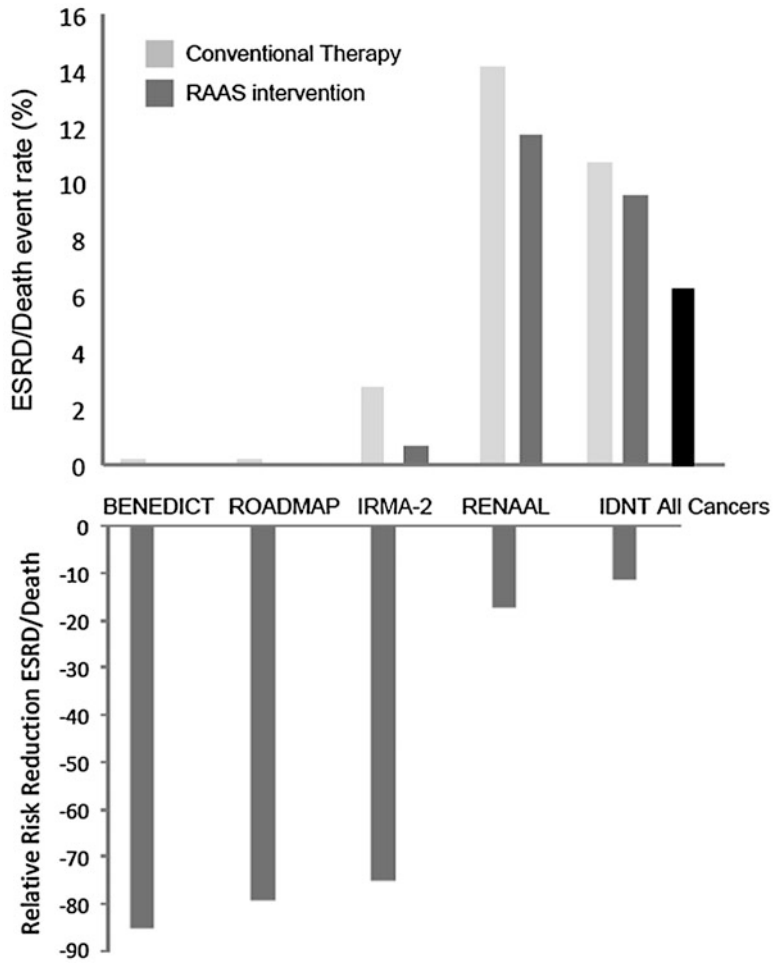


**Fig. 11** *Upper part*: comparison of death rates of patients with diabetes at early and advanced stages of diabetic nephropathy. *Bottom part*: comparison of the effect of intervention in the RAAS on ESRD at different stages of diabetic nephropathy. Early intervention appears to be most beneficial in reducing the risk of ESRD (Figure adapted from Heerspink and de Zeeuw (2011))

investigated the safety and long-term renal effects of dual RAAS blockade with an ACEi and ARB (Mann et al. 2008). Results of the ONTARGET showed that combination therapy with an ACEi and ARB had no beneficial effect on long-term renal outcomes (i.e., DSCR, ESRD, or death) (Mann et al. 2008). In contrast, long-term renal outcomes occurred significantly more frequent with dual RAAS blockade compared to monotherapy with an ACEi even though proteinuria was reduced (Mann et al. 2008).

In conclusion, although several studies have reported beneficial short-term effects of dual RAAS blockade with an ACEi and an ARB on proteinuria and blood pressure, these effects occurred at the expense of an increase in adverse events including an increase in serum potassium levels and hypotension (Roscioni et al. 2014a). These unintended (or off-target) effects may have blunted the beneficial effects of blood pressure and albuminuria lowering and may have led to more frequent occurrence of long-term renal outcomes.

## Dual RAAS Blockade: ACEi/ARB Plus DRI

In 2007, the first effective oral *direct renin inhibitor* (DRI) became available for clinical use. Direct renin inhibitors inhibit the conversion of angiotensinogen to angiotensin I at the first rate-limiting step in the RAAS cascade (Persson et al. 2011). Renin inhibition with aliskiren was associated with a decrease in albuminuria and a reduction blood pressure similar to that of monotherapy with ACEi or ARBs (Persson et al. 2008b).

Increased renin activity during long-term treatment with either ACEi or ARBs, as a result of non-ACE pathways that convert renin to angiotensin II, could limit the efficacy of ACEi and ARBs (Van Buren and Toto 2013a; Roscioni et al. 2014a). Therefore, the potential additional effects of concomitant therapy with either an ACEi or ARB and a DRI were investigated in randomized clinical trials. The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial showed that the combination of aliskiren with an ARB reduced albuminuria compared to aliskiren or ARB alone in patients with type 2 diabetes, hypertension, and proteinuria (Persson et al. 2011; Parving et al. 2008). However, this potential beneficial effect of dual RAAS blockade with either an ACEi or ARB in combination with a DRI on proteinuria did not result in a clinical, long-term beneficial effect. The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) study showed that aliskiren, compared to placebo, in addition to treatment with an ACEi or ARB, did not confer renal or cardiovascular protection despite additional blood pressure and albuminuria lowering (Parving et al. 2012). In the aliskiren arm of the ALTITUDE trial, hyperkalemia, hypotension, and acute renal impairment occurred more frequently than in the control group, and these adverse effects may have offset the renal and cardiovascular protective effects of blood pressure and albuminuria lowering (Parving et al. 2012).

## Lipid-Lowering Therapy

Although *lipid-lowering therapy* has been shown to be effective in reducing cardiovascular morbidity and mortality in diabetic patients with hyperlipidemia, the effect of lipid-lowering therapy on diabetic nephropathy has been a subject of debate for many years (Heerspink and de Zeeuw 2011; Leiter 2005). Data regarding the potential renoprotective effects of lipid-lowering therapy are relatively scarce; consequently the effects of lipid-lowering therapy on diabetic nephropathy are uncertain.

### Statins

*Statins* (HMG CoA reductase inhibitors) are competitive inhibitors of HMG CoA reductase, the rate-limiting enzyme in biosynthesis of cholesterol. Several studies have reported that statins, aside from their cholesterol-lowering effects, may have other potential pleiotropic effects. Suggested potential pleiotropic effects include a reduction of urinary protein excretion, lowered inflammatory response, and decreased interstitial fibrosis, which all could potentially improve renal function (Olyaei et al. 2011).

In a prospective, controlled study in patients with CKD, proteinuria, and hypercholesterolemia, Bianchi et al. demonstrated that the use of atorvastatin in addition to ACEi or ARBs significantly reduced *urinary protein excretion* and resulted in a slower *decline in GFR* compared to treatment with ACEi or ARBs alone (Bianchi et al. 2003). A meta-analysis of 27 RCTs demonstrated that statin therapy slightly reduced proteinuria and the rate of eGFR decline, especially in subjects with CVD (Sandhu et al. 2006). This beneficial effect appeared to be larger for atorvastatin than for other statins (Sandhu et al. 2006). However, no significant effect on renal function decline was observed in a subgroup of patients with diabetic nephropathy (Sandhu et al. 2006). A meta-analysis of Strippoli et al. reported a significant reduction in 24 h urinary protein excretion in patients with CKD receiving statins based on a subgroup analysis of 6 RCTs including 311 patients (Strippoli et al. 2008). However, in this meta-analysis, statin therapy was not found to improve GFR in subjects with CKD (Strippoli et al. 2008).

In a post hoc analysis of the Collaborative Atorvastatin Diabetes Study (CARDS), a modest improvement in annual change of estimated GFR was observed, particularly in patients with albuminuria (Colhoun et al. 2009). No effect of treatment with atorvastatin on albuminuria was detected, which could have been a result of the low baseline prevalence and incidence rate of albuminuria in the CARDS study (Colhoun et al. 2009). The Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease Trial (PLANET I)

compared the effects of atorvastatin and rosuvastatin on renal parameters in diabetic patients with proteinuria that were treated with either an ACEi or ARB. After 1 year of treatment, the use of atorvastatin was associated with a significant reduction in proteinuria, but did not considerably change the rate of renal function decline (Heerspink and de Zeeuw 2011; Olyaei et al. 2011; de Zeeuw et al. 2010; ClinicalTrials.gov 2011). The use of rosuvastatin, however, had no significant effect on proteinuria, but was associated with a decrease in estimated GFR (Heerspink and de Zeeuw 2011; de Zeeuw et al. 2010; ClinicalTrials.gov 2011). In the Study of Heart and Renal Protection (SHARP) including subjects with CKD, it was shown that the use of simvastatin/ezetimibe significantly reduced the risk of major vascular events compared to placebo (Baigent et al. 2011). However, the use of simvastatin plus ezetimibe did not result in significant reductions in renal disease progression to ESRD (Baigent et al. 2011).

In conclusion, several studies have suggested that statins may have pleiotropic effects besides a cholesterol-lowering effect including a reduction of urinary protein excretion. However, these effects appeared to be very heterogeneous for different statins (Heerspink and de Zeeuw 2011; Sandhu et al. 2006; Strippoli et al. 2008). Atorvastatin appears to have a larger beneficial effect on the rate of renal function decline than other statins (Sandhu et al. 2006). However, more studies are needed to confirm the potential beneficial effects of statins, and atorvastatin, on diabetic renal disease progression.

### Fibrates

*Fibrates* (PPARα agonists) also intervene in lipid metabolism and primarily reduce triglyceride levels and raise HDL cholesterol levels. Fibrates, besides their cardioprotective effects, also appear to have renoprotective effects in patients with diabetes. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, patients with type 2 diabetes were randomly assigned to treatment with fenofibrate or placebo for 5 years (Davis et al. 2011). Results of the FIELD trial indicated that fenofibrate reduced progression of *albuminuria* and decline of estimated GFR over time, despite an initial reversible decrease in estimated GFR (Davis et al. 2011). Furthermore, a meta-analysis of Jun et al. showed that the use of fibrates reduced the risk of progression of albuminuria in subjects with diabetes (Jun et al. 2012). Estimated GFR, however, was slightly reduced in subjects using fibrates, but the use of fibrates had no detectable effect on the risk of ESRD (Jun et al. 2012).

## Lifestyle Interventions

Several pharmacologic treatment strategies for the management of diabetes and its complications are mentioned earlier. Medical nutrition therapy, however, also plays a major role in managing diabetes and preventing, or at least slowing, the rate of development of diabetes complications (American Diabetes Association et al. 2008). Weight loss is recommended for all overweight and obese subjects with diabetes (American Diabetes Association 2012). Furthermore, we will focus on the potential beneficial effects of optimizing sodium and protein intake.

### Optimizing Body Weight

The prevalence of *obesity* (defined as a body mass index [BMI] $\geq$30 kg/m$^2$) is increasing worldwide and has more than doubled over the past 25 years (Malik et al. 2013). Obesity is an independent and important risk factor for the development of type 2 diabetes, and the increasing prevalence of diabetes is considered to be predominantly caused by the increasing prevalence of obesity (Stefan et al. 2014).

Obesity and especially a central body fat distribution or visceral adiposity are associated with an increased risk of hyperfiltration, albuminuria, decline in GFR, as well as onset and progression of CKD in the general population (Fox et al. 2004; Kwakernaak et al. 2013; Pinto-Sietsma et al. 2003). Whether obesity and a central body fat distribution also is associated with the development and progression of diabetic

nephropathy is still unclear. BMI and central obesity (measured as waist circumference) were found to be associated with albuminuria in subjects with diabetes (Wentworth et al. 2012; Kramer et al. 2009; Rossi et al. 2010; Vergouwe et al. 2010). However, data regarding the effect of central obesity and BMI on progression of diabetic nephropathy are relatively scarce. Zoppini et al. reported that annual decline of estimated GFR was higher in obese subjects with type 2 diabetes (Zoppini et al. 2012).

*Weight loss interventions*, including *bariatric surgery* and nonsurgical interventions, were found to reduce body weight, blood pressure, and urinary albumin excretion, normalize hyperfiltration, and improve renal function in patients with CKD (Neff et al. 2013; Navaneethan et al. 2009). Furthermore, it was shown that bariatric surgery, compared to nonsurgical therapy, resulted in better glucose control and more weight loss in obese patients with diabetes after a follow-up period of 1 or 2 years (Buchwald et al. 2004; Sjostrom et al. 1999; Maggard-Gibbons et al. 2013). In the Swedish Obese Subjects (SOS) study, bariatric surgery was associated with a reduction in all-cause mortality, decreased incidences of diabetes, myocardial infarction, and stroke after 10 years of follow-up (Sjostrom 2013).

Although data on the effects of bariatric surgery on diabetes-related microvascular complications are relatively scarce, several studies have reported a beneficial effect of bariatric surgery on albuminuria and microvascular complications in subjects with diabetes (Navaneethan et al. 2010; Miras et al. 2012; Amor et al. 2013). The beneficial effects of bariatric surgery on microvascular complications might, at least in part, be explained through remission of diabetes and improved glycemic control and blood pressure after bariatric surgery (Neff et al. 2013). However, these results are limited to short-term follow-up periods, and consequently, no conclusions could be drawn regarding the long-term renal outcomes of bariatric surgery in obese subjects with diabetes (Maggard-Gibbons et al. 2013; Gloy et al. 2013).

**Table 4** By the WHO recommended dietary sodium (Na) and salt (NaCl) intake and observed sodium and salt intake in subjects with diabetes and nephropathy

| | Recommended dietary intake | | Observed dietary intake | |
|---|---|---|---|---|
| | g/day | mmol/day | g/day | mmol/day |
| Sodium (Na)[a] | 2 | 87 | 4.6 | ~200[c] |
| Salt (NaCl)[b] | 5 | 85 | 11.5 | 195 |

[a]The molecular weight of sodium is 23 g/mol; 1 g of Na is equivalent to 43.5 mmol Na

[b]The molecular weight of salt is 58 g/mol; 1 g NaCl is equivalent to 17 mmol NaCl

[c]Mean observed sodium intake in patients with type 2 diabetes and nephropathy in a Dutch cohort (Kwakernaak et al. 2014)

## Optimizing Sodium Intake

The World Health Organization (WHO) recommends a dietary *sodium intake* of 2 g sodium (Na) or 5 g salt (NaCl) per day for adults (Table 4; World Health Organization (WHO) 2012). The current daily sodium intake, however, exceeds these recommendations. In a systematic analysis of 24 h sodium excretion and dietary surveys, mean global dietary sodium intake was found to be approximately 4 g per day (Powles et al. 2013), which is twice the recommended daily intake. This systematic analysis, however, only included studies that were representative of a (sub)national population; studies based exclusively on individuals with, for example, hypertension, were excluded (Powles et al. 2013). In subjects with type 2 diabetes and nephropathy in Western Europe, mean sodium intake (measured as 24 h sodium excretion) was found to be approximately 4.6 g per day (Table 4; Kwakernaak et al. 2014).

In healthy subjects, dietary sodium loading suppresses the *RAAS system*, which results in lower plasma renin, angiotensin I, angiotensin II, and aldosterone levels (Fig. 12; adapted from Charytan et al. (Charytan and Forman 2012)). In hypertensive patients with diabetes, however, it was reported that the RAAS system showed normal activation and that it was poorly suppressed during high sodium loading (Charytan and Forman 2012; Price et al. 1999).

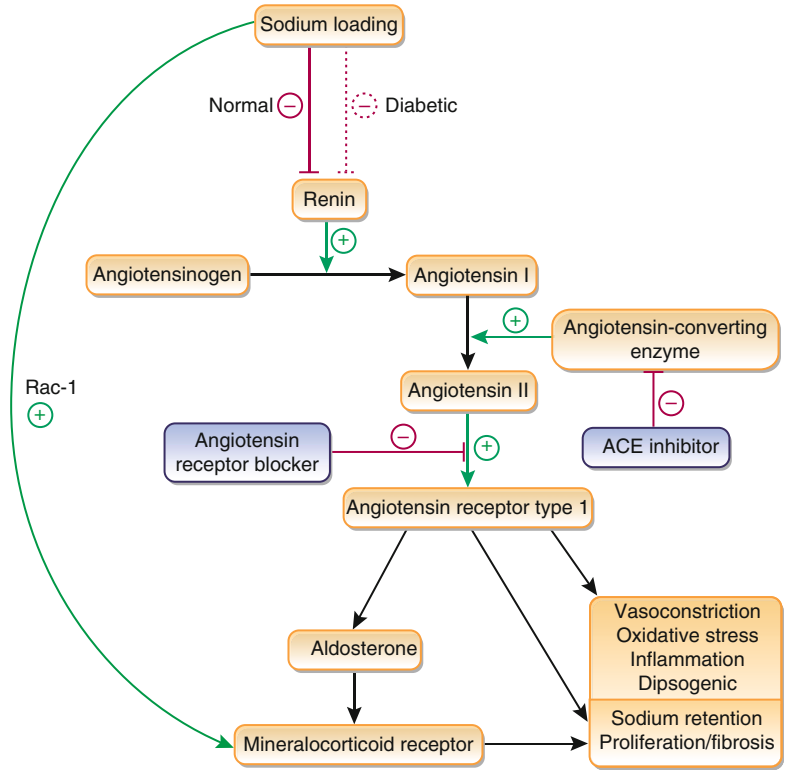


**Fig. 12** In healthy subjects, sodium loading suppresses renin synthesis, but this response may be attenuated in diabetes (Figure adapted from Charytan and Forman (2012))

It has been established that a low sodium diet potentiates the efficacy of ACEi and ARBs in patients with hypertension (Navis et al. 1987a, b), diabetes (Houlihan et al. 2002), and diabetic nephropathy (Kwakerkaak et al. 2014). Dietary sodium restriction during treatment with RAASi was found to be equally effective in reducing albuminuria as addition of hydrochlorothiazide (HCT) to RAASi in subjects with nondiabetic (Vogt et al. 2008) and diabetic nephropathy (Kwakernaak et al. 2014). Albuminuria was even further reduced when both HCT and a low sodium diet were added to treatment with ACEi (Vogt et al. 2008; Kwakernaak et al. 2014). Slagman et al. demonstrated that dietary sodium restriction to a level that is currently recommended in guidelines was more effective for reduction of proteinuria and blood pressure than dual RAAS blockade in nondiabetic nephropathy (Slagman et al. 2011). Furthermore, it was demonstrated that moderation of sodium intake also potentiates the effects of RAASi on long-term cardiovascular and renal end points in subjects with diabetic nephropathy included in the RENAAL and IDNT trials (Lambers Heerspink et al. 2012).

In conclusion, current evidence suggest that a reduction of sodium intake to levels recommended in guidelines of the WHO (i.e., 2 g sodium/day or 5 g salt/day) is sufficient to substantially enhance the beneficial effects of RAAS inhibitors (Lambers Heerspink et al. 2013).

## Optimizing Protein Intake

The optimal amount of dietary *protein intake* for subjects with diabetes and kidney disease has been a subject for debate for many years. Current guidelines of the American Diabetes Association (ADA) state that there is insufficient evidence to suggest that usual protein intake (15–20 % of total energy intake) should be modified in patients with diabetes and a normal renal function (American Diabetes Association et al. 2008). In early and later stages of diabetic kidney disease, reduction of protein intake to 0.8–1.0 g/kg and to 0.8 g/kg body weight per day, respectively, may help to slow the progression

of *albuminuria* and *renal function decline* (American Diabetes Association et al. 2008).

A meta-analysis of 10 studies investigating the effect of dietary protein restriction on progression of renal disease showed that protein restriction reduced the risk of renal failure in nondiabetic renal disease and slowed the increase in UAE and the decline in GFR in type 1 diabetic renal disease (Pedrini et al. 1996). These results were confirmed in a meta-analysis of 13 RCTs (Kasiske et al. 1998). However, the magnitude of the effect of protein restriction on renal function decline was found to be relatively small (Kasiske et al. 1998). Pijls et al. investigated the effects of dietary protein restriction to 0.8 g/kg on albuminuria in subjects with type 2 diabetes and, at least, microalbuminuria (Pijls et al. 1999). This study reported an association between protein intake and albuminuria, indicating that reduction in protein intake has beneficial effects on albuminuria (Pijls et al. 1999). However, the compliance that was achieved in this study was disappointingly low (i.e., protein intake, measured as 24 h urea excretion, was 1.1 g/kg in the low-protein group) (Pijls et al. 1999). Hansen et al. investigated the effect of further protein restriction to 0.6 g/kg per day on progression of diabetic nephropathy to ESRD in subjects with type 1 diabetes (Hansen et al. 2002). Although compliance was also not optimal in this study (i.e., protein intake was 0.9 g/kg per day in the low-protein group), this study showed beneficial effects of protein restriction on progression of diabetic nephropathy toward ESRD (Hansen et al. 2002).

In conclusion, evidence suggests that moderate protein restriction in patients with diabetic nephropathy might have beneficial effects on albuminuria and progression of diabetic nephropathy to ESRD. The magnitude of the effect, however, was found to be relatively small. Furthermore, compliance to the low-protein diet is important, but difficult to achieve.

## Cross-References

- Anatomy, Physiology and Pathophysiology of Renal Circulation
- Diseases of Renal Macrocirculation: Atherosclerosis and Renal Artery Stenosis
- Epidemiology of Atherosclerotic Vascular Diseases
- Physiology and Pathophysiology of Microcirculation

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