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An eBook on Type 2 Diabetes

Chapter 4

Diabetic Nephropathy

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1. Introduction

Diabetic nephropathy is a chronic microvascular complication of diabetes and is the single most common cause of End Stage Renal Disease (ESRD) in Europe, Japan, and the United States, with diabetes accounting for 25% to 45% of all patients enrolled into ESRD programmes. The increased mortality in proteinuric diabetic patients is due not only from end-stagerenal disease (ESRD) but also from associated cardiovascular disease, with the latter being particularly common in type 2 diabetes patients. It often starts with microalbuminuria and progresses to macro albuminuria and sometimes to overt proteinuria with a decrease in glomerular filtration over a period of time which is slow and gradual (usually a number of years) and ultimately may require renal replacement therapy.

Diabetic nephropathy occurs in both type 1 (formerly called insulin-dependent or juvenile onset) and type 2 (formerly called non-insulin-dependent or adult onset) diabetes mellitus, as well as in other secondary forms of diabetes mellitus, for example after pancreatitis or pancreatectomy.

2. Epidemiology

The overall prevalence of microalbuminuria and macroalbuminuria is around 30% to 35% in both types of diabetes and this depends on a number of factors including the population studied. The highest prevalence, exceeding 50%, is found in Native Americans, followed by Asians, Mexican Americans, blacks, and European white patients [1]. Prevalence of albuminuria decreased but that of reduced glomerular filtration rate increased in patients with diabetes between 1988 and 2014 based on cross-sectional study of 6,251 patients ≥ 20 years old with diabetes in United States who completed surveys between 1988 and 2014 (NHANES III 1988-1994, NHANES 1999-2004, and NHANES 2005-2008). Age-adjusted incidence of diabetes-

related chronic kidney disease reported a decline from 299 to 197.7 per 100,000 persons with diabetes from 1990 to 2006. Potential reasons cited for this include:

- earlier detection and better management of kidney disease
- improved treatment and care of kidney disease
- better control of risk factors such as hypertension and glycaemic control
- large increase in new cases of diabetes (more patients who have not had diabetes long enough to develop CKD) [2].

- **Type 1 diabetes**- The epidemiology of diabetic nephropathy has been best studied in patients with type 1 disease as the time of clinical onset is usually known. Approximately 20 to 30 percent will have moderately increased albuminuria, formerly called "microalbuminuria," after a mean duration of diabetes of 15 years. Less than half of these patients will progress to overt nephropathy; moderately increased albuminuria may regress or remain stable in a substantial proportion, probably related to improved glycaemic and better blood pressure control with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) [3,4].

- **Type 2 diabetes**- In Caucasians, the prevalence of progressive renal disease has generally been lower in type 2 diabetes than in type 1 disease. However, this observation may be a function of the usually later-onset disease and shorter-duration "exposure" in type 2 than type 1 diabetes. This may not, however, apply to all groups with type 2 diabetes, some of whom can have severe and progressive kidney disease and poor prognosis. Data seem to suggest that the renal risk is currently equivalent in the two types of diabetes. Evidence to support this hypothesis includes the observations that the time to proteinuria from the onset of diabetes and the time to ESRD from the onset of proteinuria was more or less similar in type 1 and type 2 diabetes [5].

2.1. Classification: Diabetic nephropathy can be classified according to a number of different subtypes:

2.1.1. Classification according to pathology (Renal pathology society classification)

- **Class I** - mild or nonspecific light microscopy changes and electron microscopy proven glomerular basement membrane thickening (isolated glomerular basement membrane thickening: basement membranes are greater than 430 nm in males older than age 9 years and 395 nm in females). There is no evidence of mesangial expansion, increased mesangial matrix, or global glomerulosclerosis involving >50 percent of glomeruli).

- **Class IIa** - mild mesangial expansion (in > 25% of observed mesangium)

- **Class IIb** - severe mesangial expansion (in > 25% of observed mesangium). A lesion is considered severe if areas of expansion larger than the mean area of a capillary lumen are present in >25 percent of the total mesangium.

- **Class III** - nodular sclerosis (at least 1 convincing Kimmelstiel-Wilson lesion) and<50 percent global glomerulosclerosis.

- **Class IV** - advanced diabetic glomerulosclerosis (global glomerular sclerosis in> 50% of glomeruli) with > 50 % glomerulosclerosis [6].

2.1.2. Classification according to severity of interstitial fibrosis and tubular lesion

- A score of 0 is assigned if the interstitium has no areas of interstitial fibrosis and tubular atrophy (IFTA); scores of 1, 2, or 3 are assigned if areas of IFTA <25, 25 to 50 or >50 percent, respectively.

- A score of 0 is assigned if no T lymphocytes or macrophage infiltrate is present. Scores of 1 or 2 are assigned if infiltrate is limited to the area surrounding atrophic tubules, or if infiltrate is not limited, respectively.

- Scores of 0, 1, or 2 are assigned if there is either no arteriolar hyalinosis, one arteriole, or more than one arteriole with hyalinosis is present. In addition, the most severely affected arteriole is assigned a score of 0, 1, or 2 if there is no intimal thickening, intimal thickening < thickness of media or intimal thickening > thickness of the media [7].

2.1.3. Classification according to glomerular filtration rate (GFR) and albuminuria category (Kidney Disease Improving Global Outcomes (KDIGO)

a] GFR categories

- G1 - GFR > 90 mL/minute/1.73 m2 (normal or high)

- G2 - GFR 60-89 mL/minute/1.73 m2 (mildly decreased compared to young adult level)

- G3a - GFR 45-59 mL/minute/1.73 m2 (mild-to-moderately decreased)

- G3b - GFR 30-44 mL/minute/1.73 m2 (moderate-to-severely decreased)

- G4 - GFR 15-29 mL/minute/1.73 m2 (severely decreased)

- G5 - GFR < 15 mL/minute/1.73 m2 (kidney failure)

b) Albuminuria categories

- A1 - albumin excretion rate (AER) < 30 mg/24 hours, albumin to creatinine ratio (ACR) < 30 mg/g (3 mg/mmol) (normal-to-mildly increased proteinuria)
- A2 - AER 30-300 mg/24 hours, ACR 30-300 mg/g (3-30 mg/mmol) (moderately increased proteinuria)
- A3 - AER > 300 mg/24 hours, ACR > 300 mg/g (30 mg/mmol) (severely increased proteinuria [including nephrotic syndrome]) [8].

2.2. Risk factors

There are a number of risk factors for the development of diabetic nephropathy. Some of the more likely factors are:

Genetic susceptibility: Genetic susceptibility is an important determinant of both the incidence and severity of diabetic nephropathy. The likelihood of developing diabetic nephropathy is increased in patients with a diabetic sibling or parent who has diabetic nephropathy; these observations have been made in both type 1 and type 2 diabetes patients [9].

Race: The incidence and severity of diabetic nephropathy is increased in the Afro-Caribbean population (3- to 6-fold increment compared to Caucasians), Mexican-Americans, and Pima Indians with type 2 diabetes. This observation in such genetically disparate populations suggests a primary role of socio-economic factors, such as diet as well as poor control of hyperglycaemia, hypertension, and obesity [10].

Age: The impact of age at onset of diabetes on the risk of developing nephropathy and end-stage renal disease is unclear. As an example, among patients with type 2 diabetes (but not type 1), increasing age, along with increasing duration of diabetes, has been associated with an increased risk for developing albuminuria in an Australian population [11].

Hypertension: Many prospective studies have noted an association between the development of diabetic nephropathy and higher systemic blood pressures [12].

Glomerular filtration rate: Those patients with glomerular hyperfiltration appear to be at increased risk for diabetic renal disease. This is particularly true for overt nephropathy if the initial GFR is above 150 mL/min; by comparison, lesser degrees of hyperfiltration may have a slower course of nephropathy development [13].

Poorly controlled diabetes it is a well-established fact that poor glycaemic control is associated with earlier onset of overt nephropathy development and this has been proven in several different studies [14].

Smoking: Smoking increases albuminuria and the risk of end-stage renal disease. It also has been shown to decrease survival once patients are on dialysis [15].

Obesity - A high body mass index (BMI) has been associated with an increased risk of chronic kidney disease among patients with diabetes. Diet and weight loss has been shown to reduce albuminuria and improve kidney function in such patients [16].

Oral Contraceptive Pill (OCP) - There has been a suggested link between oral contraceptive use and the risk of development of diabetic nephropathy in one report [17].

Hypercholesterolemia - Poorly controlled cholesterol level is also associated with adverse prognosis related to diabetic kidney disease [18].

Persistently increased albuminuria: Severely increased albuminuria, formerly called "macro-albuminuria," is strongly associated with and predictsfuture development of severe nephropathy with decreased eGFR [19].

Acute kidney injury: Acute kidney injury is associated with increased future risk of developing advanced chronic kidney disease in patients with diabetes [20].

Vitamin D deficiency: This may be associated with increased risk of diabetic nephropathy. This is based on a cross-sectional study of 1,216 adults ≥ 20 years old with diabetes who were evaluated for vitamin D deficiency and insufficiency and occurrence of diabetic nephropathy - nephropathy was seen in 30.7% of those who were Vitamin D deficient or insufficient [21].

3. Relationship between Retinopathy/Neuropathy and Diabetic Nephropathy

Patients with nephropathy and type 1 diabetes almost always have other signs of diabetic microvascular disease, such as retinopathy and neuropathy. Retinopathy is easy to detect clinically, and typically precedes the onset of overt nephropathy in these patients. The converse is not true. Type 2 diabetes patients with marked proteinuria and retinopathy most likely have diabetic nephropathy, while those without retinopathy tend to have a high frequency of nondiabetic kidney disease. Blindness due to severe proliferative retinopathy or maculopathy is approximately five times more frequent in types 1 and 2 diabetic patients with nephropathy than in normoalbuminuric patients. Macroangiopathies (e.g., stroke, carotid artery stenosis, coronary heart disease, peripheral vascular disease) are two to five times more common in patients with diabetic nephropathy and, as stated earlier, macroangiopathy is the major cause of mortality rather than ESKD for patients with diabetic nephropathy [22]. Peripheral neuropathy is present in almost all patients with advanced nephropathy. Foot ulcers with sepsis leading to amputation occur frequently (>25% of cases), probably due to a combination of neural and arterial diseases. Autonomic neuropathy may be asymptomatic and manifest simply as abnor-

mal cardiovascular reflexes, or it may result in debilitating symptoms. Almost all patients with nephropathy have grossly abnormal results on autonomic function tests [23].

4. Nondiabetic Kidney Disease

Proteinuria and/or haematuria in diabetes mellitus is occasionally due to a glomerular disease other than diabetic nephropathy. Examples include membranous nephropathy, minimal change disease, IgA nephropathy, focal segmental glomerulosclerosis, Henoch-Schönlein purpura (IgA vasculitis), thin basement membrane disease, proliferative glomerulonephritis, collapsing glomerulopathy, and pauci-immune crescentic glomerulonephritis. With regards to membranous nephropathy, porcine insulin has been implicated to be an inciting antigen in some patients.

When to suspect non-diabetic kidney disease?

1. Onset of proteinuria less than five years from the documented onset of type 1 diabetes

2. Acute onset of renal disease.

3. The presence of an active urine sediment containing red cells (particularly acanthocytes) and cellular casts. However, haematuria and red cell casts can also be occasionally seen in diabetic nephropathy.

4. Absence of retinopathy or neuropathy [24].

5. Pathogenesis

There are a number of mechanisms by which hyperglycemia triggers the basic pathogenic changes in diabetic nephropathy. Listed below are some common immune triggers and markers:

Hyperglycaemia may directly induce mesangial expansion and injury, perhaps in part via increased matrix production or glycation of matrix proteins. In vitro studies have demonstrated that hyperglycaemia stimulates mesangial cell matrix production and mesangial cell apoptosis. Glomerulosclerosis may result from intra glomerular hypertension induced by renal vasodilatation, or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli. The role of glomerular hypertension and hyperfiltration in diabetic nephropathy is reinforced by the apparent benefits of blockade of the renin-angiotensin system. Antagonizing the profibrotic effects of angiotensin II may also be a significant factor in benefits observed with these agents [25].

Glycation of tissue proteins also may contribute to the development of diabetic nephropathy and other microvascular complications. In chronic hyperglycemia, some of the excess

glucose combines with free amino acids on circulating or tissue proteins. This non-enzymatic process initially forms reversible early glycation products and, later, irreversible advanced glycation end products (AGEs). Circulating AGE levels are increased in diabetes, particularly those with renal insufficiency, since AGEs are normally excreted in the urine. The net effect is tissue accumulation of AGEs, in part by crosslinking with collagen, which can contribute to the associated renal and microvascular complications. Other proposed mechanisms by which hyperglycaemia might promote development of diabetic nephropathy include activation of protein kinase C, and upregulation of heparanase expression.

Activation of cytokines, profibrotic elements, inflammation, and vascular growth factors (vascular endothelial growth factor, VEGF) may be involved in the matrix accumulation in diabetic nephropathy. A potentially pathogenic role for VEGF in diabetic nephropathy is supported by the observation that VEGF blockade improves albuminuria in experimental models of diabetic nephropathy [26]. Hyperglycaemia also increases the expression of transforming growth factor-beta (TGF-beta) in the glomeruli and diabetes is associated with decreased expression of renal bone morphogenic protein-7 (BMP-7), which appears to counter the profibrogenic actions of TGF-beta [27]. It has been shown that the administration of hepatocyte growth factor, which specifically blocks the profibrotic actions of TGF-beta, ameliorates diabetic nephropathy in mice. Renal expression of nephrin may be impaired in diabetic nephropathy. When compared with nondiabetic patients with minimal change nephropathy and controls, patients with diabetic nephropathy had markedly lower renal nephrin expression [28].

Defects in podocyte-specific insulin signalling may contribute to diabetic nephropathy. Mouse models have been generated in which the gene encoding the insulin receptor is deleted in a podocyte-specific manner.

6. Comparison of Nephropathy between Type 1 and Type 2 diabetes:

- Renal pathology and structural-functional relationships has been less well studied in type 2 diabetes patients, despite more than 80% of diabetes patients with ESRD have type 2 diabetes.

- Proteinuric white Danish patients with type 2 diabetes were reported to have structural changes similar to those of proteinuric patients with type 1 diabetes, and the severity of these changes was strongly correlated with the subsequent rate of decline of GFR; however, the study also noted that some proteinuric patients with type 2 diabetes had little or no evidence of diabetic glomerulopathy.

- A study of 52 type 2 diabetic patients from Northern Italy who underwent biopsy for clinical indications described greater heterogeneity in renal structure, with one third having

nondiabetic renal diseases.

• In a Danish study, 75% of unselected proteinuric type 2 diabetic patients had histological evidence of diabetic nephropathy but 25% had a variety of nondiabetic glomerulopathies, including minimal lesions, glomerulonephritis, mixed diabetic and glomerulonephritis changes, and chronic glomerulonephritis [29]. Marked heterogeneity in renal histopathological structure is present in type 2 diabetic patients with increased proteinuria.

• Only a minority of patients have histopathologic patterns resembling those typically present in patients with type 1 diabetes; the typical pattern is 30% of patients with microalbuminuria and 50% of those with proteinuria. The remainder have minimal renal abnormalities or tubulo-interstitial, vascular, and global glomerulosclerotic changes, which are disproportionally severe relative to the diabetic glomerulopathy lesions (atypical pattern, about 40% of patients with microalbuminuria and proteinuria).

• In type 2 diabetes, a reduced GFR in the presence of a normal albumin excretion rate is a common finding. Ekinci and colleagues have recently described that among normoalbuminuric type 2 diabetic patients with impaired renal function, only a subset had typical diabetic glomerulopathy, whereas the remaining patients had predominantly tubulo-interstitial and vascular changes [30].

• Most studies dealing with the natural history of diabetic nephropathy have demonstrated a relentless, often linear rate of decline in GFR. Importantly, this rate of decline is highly variable across individuals, ranging from 2 to 20 mL/min/yr, with a mean of about 12 mL/min/yr. Type 2 diabetes patients with nephropathy display the same degree of loss in filtration function and variability of GFR.

7. Other Renal Pathology found in Patients with Diabetes

• Minimal change nephrotic syndrome and membranous nephropathy occur with greater frequency in patients with type 1 diabetes than in nondiabetic persons.

• Fewer than 1% of patients with type 1 diabetes for 10 years or longer and fewer than 4% of those with proteinuria and long duration of diabetes will be found to have conditions other than, or in addition to, diabetic nephropathy.

• Proteinuric type 2 diabetic patients without retinopathy may have a high incidence of atypical renal biopsy findings or other diseases. Proteinuric patients with type 1 diabetes of less than 10 years' duration and type 2 diabetic patients without retinopathy should be thoroughly evaluated for other renal diseases, and a renal biopsy is strongly considered.

- **Other causes of nodular glomerulosclerosis**:

  - Dysproteinemias such as amyloidosis and monoclonal immunoglobulin deposition diseases (MIDD), mostly kappa light chain deposition disease.

  - Organized glomerular deposition diseases, fibrillary and immunotactoid glomerulonephritis, fibronectin glomerulopathy, and collagen III glomerulopathy.

  - Chronic hypoxic or ischemic conditions, such as cyanotic congenital heart disease, Takayasu's arteritis with renal artery stenosis, or cystic fibrosis

  - Chronic membrano-proliferative glomerulonephritis (type I)

  - Idiopathic nodular glomerulosclerosis, which is frequently associated with smoking, hypertension and metabolic syndrome, but without overt diabetes mellitus [31].

8. Reversibility of Diabetic Nephropathy Lesion

Mesangial expansion present after 7 months of diabetes was reversed within 2 months after normoglycemia was induced by islet transplantation in rats with streptozotocin-induced diabetes. But it was disappointing to note that no improvement in diabetic nephropathy lesions in their native kidneys was found after 5 years of normoglycemia following successful pancreatic transplantation in type 1 patients with a diabetes duration of approximately 20 years. After 10 years of normoglycemia, however, these same patients showed marked reversal of diabetic glomerulopathy lesions. Thus, GBM and TBM width were reduced at 10 years compared with the baseline and 5-year values, with several patients having values at 10 years that had returned to the normal range; primarily due to a marked decrease in mesangial matrix fractional volume. Remarkable glomerular architectural remodelling was seen by light microscopy, including the complete disappearance of Kimmelstiel-Wilson nodular lesions. The reason for the long delay in this reversal process is not understood but could include epigenetic memory of the diabetic state, the slow process of replacement of glycated by nonglycated ECM, or other as yet undetermined processes. More recently, remodelling and healing in the tubulo-interstitium has also been demonstrated in these same patients. These studies have demonstrated reduction in total cortical interstitial collagen and underscore the remarkable potential for healing of kidney tissue that has been damaged by long-standing diabetes. Blockade of the renin angiotensin aldosterone system (RAAS) for 5 years did not lead to regression or slowing of the progression of diabetic glomerulopathy lesions in young patients with type 1 diabetes and normoalbuminuria. Whether healing can be induced by treatments other than cure of the diabetic state is currently unknown [32].

9. Diabetic Nephropathy and Hypertension

• Several studies have demonstrated blood pressure elevation in children and adults with type 1 diabetes and microalbuminuria.

• The prevalence of arterial hypertension (according to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [33] criterion of ≥140/90 mm Hg) in adult patients with type 1 diabetes increases with urine albumin level, and prevalence rates reported are 42%, 52%, and 79% in those with normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively.

• The prevalence of hypertension in those with type 2 diabetes (mean age, 60 years) was reported to be higher in comparison —71%, 90%, and 93% in the normoalbuminuria, microalbuminuria, and macroalbuminuric groups, respectively.

• A genetic predisposition to hypertension in type 1 diabetes patients who develop diabetic nephropathy has been suggested, but other studies have not confirmed this. The original finding was confirmed by using 24-hour blood pressure monitoring in a large group of parents of type 1 diabetic patients, with and without diabetic nephropathy [33].

• The cumulative incidence of hypertension was found to be higher among parents of proteinuric patients, with a shift toward a younger age at the onset of hypertension in this parental group. However, the difference in prevalence of parental hypertension was not evident when office blood pressure measurements were used.

• Several studies have reported that sodium and water retention play a dominant role in the initiation and maintenance of systemic hypertension in patients with microalbuminuria and diabetic nephropathy, whereas the contribution of the RAAS is somewhat smaller [33].

10. Albuminuria

• A preclinical phase of diabetic nephropathy consisting of a normoalbuminuric and microalbuminuric stage and a clinical phase characterized by albuminuria has been well documented in both types 1 and 2 diabetic patients.

10.1. Normoalbuminuria

• Approximately one third of type 1 diabetic patients will have a GFR above the upper normal range for age-matched healthy nondiabetic subjects. The degree of hyperfiltration is less in type 2 diabetic patients, and hyperfiltration is even reported to be lacking in some studies [34].

• The GFR elevation is particularly pronounced in patients with newly diagnosed

diabetes and during other intervals with poor metabolic control. Intensified insulin treatment and control to near-normal blood glucose levels reduces the GFR toward normal levels after a period of days to weeks in both types 1 and 2 diabetes patients

- Four factors seem to regulate GFR. Firstly, the glomerular plasma flow influences the mean ultrafiltration pressure and there by GFR. Enhanced renal plasma flow has been demonstrated in both types 1 and 2 diabetic patients with elevated GFR. Secondly, GFR is also regulated by the systemic oncotic pressure, which is reported to be normal in diabetes as calculated from plasma protein concentrations. The third determinant of GFR is the glomerular trans-capillary hydraulic pressure difference, which cannot be measured in humans. However, the demonstrated increase in filtration fraction is compatible with an enhanced transglomerular hydraulic pressure difference. The last determinant of GFR is the glomerular ultrafiltration coefficient, [Kf], which is determined by the product of the hydraulic conductance of the glomerular capillary and the glomerular capillary surface area available for filtration. Total glomerular capillary surface area is clearly increased at the onset of human diabetes.

- Longitudinal studies have suggested that hyperfiltration is a risk factor for subsequent increase in urinary albumin excretion and development of diabetic nephropathy in type 1 diabetic patients, but conflicting results have also been reported.

- The prognostic significance of hyperfiltration in type 2 diabetic patients is still debated. Six prospective cohort studies following normoalbuminuric types 1 and 2 diabetic patients for 4 to 10 years revealed that slight elevation of urinary albumin excretion, which remained in the normal range and poor glycemic control, hyperfiltration, elevated arterial blood pressure, retinopathy, and smoking contribute to the development of persistent microalbuminuria and overt diabetic nephropathy [35].

- For reasons that are not well understood, the degree of albuminuria is not necessarily linked to disease progression in patients with diabetic nephropathy in both type 1 or type 2 diabetes. This was illustrated in a report of 79 patients with type 1 diabetes from the Joslin Kidney Study who were followed for a mean of 12 years after the onset of moderately increased albuminuria [36].

- Recently, an elevated serum uric acid level was found to be a predictor of the development of diabetic nephropathy in type 1 diabetic patients, and a multicentre study has been initiated to study whether lowering uric acid in patients with early diabetic nephropathy preserves renal function.

10.2. Moderately increased albuminuria

- Recently, for CKD in general, it has been suggested to use the term moderately *in-*

creased albuminuria [37] *instead* of microalbuminuria. In addition to hyperglycemia, many other factors can induce microalbuminuria in diabetic patients, such as hypertension, obesity, heavy exercise, various acute or chronic illnesses, and cardiac failure.

• The demonstration that microalbuminuria diminishes promptly with acute reduction in arterial blood pressure argues that reversible hemodynamic factors play an important role in the pathogenesis of microalbuminuria. Imanishi and colleagues have demonstrated that glomerular hypertension is present in type 2 diabetic patients with early nephropathy and is closely correlated with increased urinary albumin excretion. In addition, increased pressure has been demonstrated in the nail fold capillaries of microalbuminuric type 1 diabetic patients.

• GFR, measured using the single-injection, chromium-51–radiolabelled ethylenediaminetetraacetic acid (51Cr-EDTA) plasma clearance method or renal clearance of inulin is normal or slightly elevated in type 1 diabetic patients with microalbuminuria. Prospective studies have demonstrated that GFR remains stable at normal or supranormal levels for at least 5 years if clinical nephropathy does not develop. Nephromegaly is still present and is even more pronounced in micro-albuminuric than in normo-albuminuric type 1 diabetic patients. In microalbuminuric type 2 patients, GFR declines at rates of about 3 to 4 mL/min/yr.

11. Haematuria

• The urine sediment in diabetic nephropathy is usually bland and haematuria is unusual in diabetes. However, microscopic haematuria can occur as it can in any form of glomerular disease, including disorders such as membranous nephropathy that are not associated with glomerulonephritis. This is an important issue in diabetic nephropathy since nondiabetic renal disease, either alone or with diabetic nephropathy, is occasionally seen in patients with diabetes.

• Red blood cell casts have also been described in patients with diabetic nephropathy. The clinical significance of this finding was evaluated in a study of eight patients with haematuria, red blood cell casts, and known diabetes for 6 to 18 years. Renal biopsy, including immunofluorescence and electron microscopy, revealed glomerulonephritis in three (post-infectious in two and IgA nephropathy in one). The other five patients had only diabetic nephropathy.

11.1. Making the diagnosis

One needs to consider a diagnosis of diabetic kidney disease patients with diabetes with any of the following:

Albuminuria of > 300 mg/24 hours or albumin to creatinine ratio > 300 mg/g (also called macroalbuminuria) [38]. It has been suggested that adjusting the urinary albumin concentration for urinary creatinine concentration may not only correct for diuresis, but elevated

ratios may reflect two independent risk factors-elevated albumin excretion, reflecting renal and vascular damage, and reduced creatinine excretion, associated with reduced muscle mass.The excretion of albumin in the urine is determined by the amount filtered across the glomerular capillary barrier and the amount reabsorbed by the tubular cells. A normal urinary β2 -microglobulin excretion rate in microalbuminuria suggests that albumin is derived from enhanced glomerular leakage rather than from reduced tubular reabsorption of protein.

Albuminuria of 30-300 mg/24 hours or albumin to creatinine ratio 30-300 mg/g (also called microalbuminuria) plus retinopathy.

Microalbuminuria plus type 1 diabetes of ≥ 10 years duration- the daily variation in urinary AER is high, 30% to 50%. Consequently, more than one urine sample is needed to determine whether an individual patient has persistent microalbuminuria. Urinary albumin excretion in the micro-albuminuric range (30 to 300 mg/24 hr) in at least two of three consecutive nonketotic sterile urine samples is the generally accepted definition of persistent microalbuminuria. For convenience, it has been recommended to use early morning spot urine samples for screening and monitoring.

Albuminuria based on elevated albumin to creatinine ratio should be confirmed with additional 2 first-voided urine specimens during subsequent 3-6 months. Determination of the IgG/IgG 4 ratio suggests that loss of glomerular charge selectivity precedes or accompanies the formation of new glomerular macromolecular pathways in the development of diabetic nephropathy. Reduction in the negatively charged moieties of the glomerular capillary wall, particularly sialic acid and heparan sulphate, has been suggested, but not all studies have confirmed these findings [39].

Consider nondiabetic causes of chronic kidney disease if any of the following are present:

- absence of diabetic retinopathy
- low or rapidly decreasing glomerular filtration rate
- rapidly increasing proteinuria or nephrotic syndrome
- refractory hypertension
- active urinary sediment
- signs or symptoms of other systemic disease
- > 30% reduction in glomerular filtration rate within 2-3 months after starting angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy

Causes of transient increases in albuminuria include:

- fever
- high-salt diet
- vigorous exercise in previous 24 hours
- infection
- dehydration
- heart failure

12. Investigations

Annual screening for diabetic kidney disease is recommended startingat diagnosis with type 2 diabetes and ≥ 5 years after diagnosis with type 1 diabetes. Screening should includemeasurement of urinary albumin to creatinine ratio (ACR) in spot urine sample and measurement of serum creatinine and estimation of estimated glomerular filtration rate (eGFR). Additional testing should be done if abnormal urine albumin excretion is present persistently: this may include confirmation first by 2 additional urine specimen testing for ACRwithin 1-2 months, tests to rule out nondiabetic causes of kidney disease if suspicion exists and kidney biopsy if uncertainty exists about the exact diagnosis.

13. Monitoring Blood Glucose Control in Patients with Chronic Kidney Disease

National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) suggests using HbA1c to measure blood sugar control in patients with CKD and diabetes. However, HbA1C may not be reflective of glucose control in people with CKD who have reduced red cell life span, and thus should be interpreted with caution; reviewing blood sugar daily logs may be more reliable. Albumin corrected fructosamine was reported to reliably indicate glycaemic control in 30 patients with diabetes and CKD stages 3-4 but HbA1c underestimated glycaemic control. Glycated albumin is reported to more accurately reflect glycaemic control compared to fructosamine and HbA1c in 25 patients with diabetes and CKD stage 4-5. Glycated albumin was also found to better estimate glycaemic control than HbA1c detected in a study in 25 patients with diabetes on haemodialysis. HbA1c and albumin-corrected fructosaminehas been reported to reliably indicate glycaemic control in patients with diabetes on peritoneal dialysis.

14. Kidney Biopsy and Pathology

Kidney biopsy is not often required but may be occasionally undertaken to definitely

diagnose diabetic glomerulopathy (possibility exists of serious diabetic glomerular lesions in patients with normoalbuminuria and normal glomerular filtration rate) in patients with a suspicion of non-diabetic kidney pathology. Typical findings in patients with type 1 diabetes and macroalbuminuriamay include increased mesangial volume and glomerular basement membrane (GBM) thickness. Tubulo-interstitial pathology findings in patients with type 1 diabetes and microalbuminuria are generally less severe. In patients with type 2 diabetes and microalbuminuria, about 40% show changes similar to type 1 diabetes, 30% show tubulo-interstitial, vascular, and/or glomerulosclerotic lesions unrelated to classic diabetic glomerulopathy and about 30% have normal or near normal biopsy results.

15. Treatment

15.1. Protein restriction

American Diabetes Association (ADA) recommendations [40] on protein intake in patients with diabetes and diabetic kidney disease recommends normal daily protein allowance (0.8 g/kg/day) for patients with non-dialysis dependent diabetic nephropathy and a higher protein intake for patients on dialysis. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) recommends target dietary protein intake 0.8 g/kg/day for people with diabetes and chronic kidney disease stages 1-4. Protein-restricted diet may slightly slow progression of diabetic nephropathy and might reduce risk of end-stage kidney disease or death. Low-protein diet may reduce proteinuria and HbA1c but may not improve glomerular filtration rate. Reducing animal protein in diet may improve cardiovascular risk measures and might improve markers of kidney function.

A low-carbohydrate, low-iron diet enriched with polyphenols may delay progression of nephropathy and reduce composite outcome of kidney replacement therapy or death compared to conventional protein-restricted diet in patients with type 2 diabetes.

15.2. Salt intake and proteinuria

A high salt intake has been shown to blunt the antiproteinuric effects of angiotensin inhibitors in patients with nondiabetic kidney disease. Salt restriction and/or diuretics enhance the effect of renin-angiotensin blockade on proteinuria in these patients. Thus, patients on ACE inhibitors or ARBs who do not have sufficient reduction in proteinuria despite appropriate blood pressure goals should be instructed to take a low-sodium diet. An assessment of baseline sodium intake can be undertaken by obtaining a 24-hour urine for sodium and creatinine. This can be repeated after several months on the low-sodium diet to determine the actual sodium intake if there is insufficient reduction in proteinuria. Salt restriction to ≤70 meq/day has been found to enhance the antiproteinuric effects of ARB in patients with type 2 diabetes. However, this degree of restriction may be difficult to achieve and maintain, and it is recom-

mended restricting sodium intake to approximately ≤100 meq/day. If a low-sodium diet is not possible, administration of a diuretic partially corrects the loss of antiproteinuric effect due to a high sodium intake [3,40].

15.3. Glycaemic control

HbA1c target < 7% (53mmol/mol) has been recommended for most nonpregnant adults with type 1 or type 2 diabetes [41], but goals should be individualized. HbA1c about 7% (53mmol/mol) is recommended to prevent or delay progression of microvascular complications of diabetes including diabetic nephropathy. One may need to consider more stringent target (such as < 6.5% or 48mmol/mol) in selected patients (early in disease course) if achievable without significant hypoglycaemia or other adverse effects. Less stringent target (such as < 8% or 64mmol/mol) may be appropriate for patients with risk for hypoglycemia, comorbidities, or limited life expectancy.

In the Diabetes Control and Complications Trial (DCCT) [42], intensive therapy reduced the occurrence of microalbuminuria by 39% (95% CI, 0.21 to 0.52), and that of albuminuria by 54% (95% CI, 0.19 to 0.74) when the primary and secondary prevention cohorts were combined for analysis.

With further follow-up of DCCT patients in the Epidemiology of Diabetes Interventions and Complications (EDIC) study [42], it was demonstrated that the reduction in the development of microalbuminuria and albuminuria translated into a 50% reduced risk (95% CI, 0.18 to 0.69; P = 0.006) of development of impaired renal function (eGFR < 60).

In Japanese type 2 diabetic patients, a beneficial impact of strict glycaemic control on the progression of normoalbuminuria to microalbuminuria and macroalbuminuria was also demonstrated in a small study with a design similar to that of the DCCT.

Results of this study have been confirmed and extended by data from the UK Prospective Diabetes Study (UKPDS) [43] documenting a progressively beneficial effect of intensive metabolic control on the development of microalbuminuria and overt proteinuria, and a 10-year post study follow-up demonstrated a long-lasting beneficial effect. This beneficial effect was confirmed in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study [44], in which 11,140 patients with type 2 diabetes were followed for a median of 5 years and a 21% reduction in the development of nephropathy (95% CI, 0.07 to 0.34) was seen in patients randomly assigned to strict glycemic control. The same trend was seen in the smaller Veterans Affair Diabetes Trial [45], but the values did not reach statistical significance.

15.4. Insulin

Intensive insulin therapy may delay onset of and slow progression of microalbuminuria and albuminuria (reduced risk of increased serum creatinine, albuminuria, and hypertension may continue 7-8 years after intensive therapy). This is based on evidence from the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Intervention and Complications (EDIC) observation findings of long-term benefit of initial intensive control referred to as metabolic memory. It is advisable to monitor blood glucose levels closely in patients with worsening kidney function and adjust dose of appropriate medications as needed to avoid hypoglycaemia.

15.5. Benefits of intensive insulin therapy

It can partially reverse the glomerular hypertrophy and hyperfiltration (both in the basal state and after a protein load) that are thought to be important risk factors for glomerular injury. It can delay the development of elevated albumin excretion. Intensive therapy to near-normal glycaemia reduces the onset or progression of diabetic nephropathy for years after less intensive therapy. It can stabilize or decrease protein excretion in patients with increased albumin excretion, although this effect may not be apparent until relative normoglycemia has been maintained for about two years. Furthermore, the restoration of eu-glycaemia with pancreas transplantation in patients with type 1 diabetes prevents recurrent nephropathy in a renal allograft.It can slow the progression of glomerular filtration rate (GFR) decline.Studies suggest that strict glycaemic control may also slow the rate of progressive renal injury even after overt dipstick-positive proteinuria has developed.

15.6. Metformin

Metformin is contraindicated in renal failure when eGFR is less than 30ml/min (dose needs to be reduced to 1gm/day when eGFR is between 30-45ml/min). Risk of lactic acidosis is present but probably over-exaggerated [42].

15.7. Sulfonylureas

First-generation sulfonylureas (chlorpropamide) have been associated with prolonged and severe hypoglycemia in patients with poor kidney function. They may also aggravate heart failure or fluid retention (antidiuretic effect) and may cause syndrome of inappropriate antidiuretic hormone.

Second generation sulfonylurea as like gliclazide and glipizide elimination half-life is generally not affected by renal dysfunction. They are the sulfonylureas of choice in patients with advanced kidney disease dosage but adjustment may be necessary to avoid hypoglycaemia. With glyburide, there is increased risk of hypoglycemia in patients with kidney failure

and patients with advanced chronic kidney disease due to increased half-life.

Third generation sulphonylureas like glimeperide needs dose reduction in patients with decreased GFR and prolonged hypoglycemia has been reported in patients with renal dysfunction.

15.8. Thiazolidinediones (glitazones)

Pioglitazone does not need dose adjustment needed in patients with poor renal reserve and can be used even in patients with stage 5 CKD. In the setting of renal failure, caution is needed against heart failure and fluid retention.

15.9. Meglitinides

Repaglinide half-life is increased with kidney dysfunction and in patients on dialysis. No dose reduction is needed with chronic kidney disease, caution is advised with kidney impairment. Nateglinide has been associated with hypoglycemia in patients with low GFR and should be used cautiously in patients with kidney disease.

15.10. Dipeptidyl peptidase IV (DPP-4) inhibitors (Gliptins)

Gliptins are safe to be used in renal impairment. Whereas no dose reduction is required with linagliptin (mostly excreted in bile)- dosage adjustment is advocated with most other gliptins like sitagliptin, saxagliptin, alogliptin and vildagliptin as all these are predominantly renally excreted [46].

15.11. Glucagon-like peptide-1 (GLP-1) receptor agonists

Exenatide should be avoided if creatinine clearance < 30 mL/minute. Liraglutide can be used up to an eGFR of 30ml/min but caution is required when initiating or escalating dose in patients with renal failure. Once weekly dulaglutide has also got license to be used up to an eGFR of 30ml/min [47].

15.12. Sodium-glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 inhibitors as a class in patients with renal impairment is not recommended when eGFR is less than 60 ml/min although recent trial EMPA-REG has shown some benefit in proteinuria reduction and slowing progression in CKD when used in patients with eGFR < 60ml/min [48].

16. Blood Pressure Control

Blood pressure targets in patients with diabetes varies, and can range from < 130/80 mm Hg to < 140/90 mm Hg. However, most of these BP recommendations are not specific to

patients with diabetes and chronic kidney disease (CKD). National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines recommend target blood pressure < 130/80 mm Hg for patients with diabetes and chronic kidney disease. Kidney Disease: Improving Global Outcomes (KDIGO) guideline for adults with chronic kidney disease and diabetes recommend target blood pressure ≤ 140/90 mm Hg if urine albumin excretion < 30 mg/24 hours and ≤ 130/80 mm Hg if urine albumin excretion > 30 mg/24 hours. American Diabetes Association (ADA) recommends systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg to reduce risk or slow progression of diabetic kidney disease. Eighth Joint National Committee (JNC 8) recommends target blood pressure < 140/90 mm Hg for patients with diabetes (JNC8 Expert opinion) and for patients with chronic kidney disease but did not make recommendation specific to combination of diabetes and chronic kidney disease [49].

- Angiotens in-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be used in patients with diabetes if

- urinary albumin excretion ≥ 300 mg/day

- consider use if urinary albumin excretion 30-299 mg/day

- urine albumin to creatinine ratio ≥ 30 mg/g

- chronic kidney disease and hypertension.

- Monitor serum creatinine and potassium levels periodically for worsening of serum creatinine and hyperkalaemia if using ACE inhibitors, ARBs, or diuretics. Consider using diuretic, calcium channel blocker, or beta blockers if additional therapy needed to control blood pressure or if patient unable to tolerate ACE inhibitors or ARBs

- In pregnant women with diabetes and chronic kidney disease (NKF KDOQI), ACE inhibitors and ARBs before pregnancy may improve foetal and maternal outcomes, but discontinue as soon as a menstrual period is missed or after a positive pregnancy test. Use insulin to control hyperglycaemia if pharmacologic therapy needed.

- Canadian Society of Nephrology [50] recommends against prescribing angiotensin converting enzyme (ACE) inhibitors in combination with angiotensin II receptor blockers (ARBs) for the treatment of hypertension, diabetic nephropathy and heart failure.

17. Angiotensin-Converting Enzyme (ACE) Inhibitors and ARB

The summary of all the trial evidence regarding the benefits of ACE inhibitor and ARBs are as follows:

• The **DIRECT study** did not show any significant effect on the incidence of microalbuminuria [51].

• The **BENEDICT study** has demonstrated that use of an ACE inhibitor, alone or in combination with a calcium channel blocker, decreases the incidence of microalbuminuria in hypertensive type 2 diabetic patients with normoalbuminuria [52]. The effect of the calcium channel block verapamil alone was similar to that of placebo.

• In the **ADVANCE study**, which included type 2 diabetic patients with or without hypertension, the fixed combination of perindopril and the diuretic indapamide reduced blood pressureand new-onset microalbuminuria by 21% [44].

• The Randomized Olmesartan and Diabetes Microalbuminuria Prevention **(ROADMAP) study** tested whether the angiotensin II receptor blocker olmesartan would reduce development of microalbuminuria in 4447 mostly hypertensive type 2 diabetic patients with normoalbuminuria. Overall, there were slightly fewer cardiovascular events with olmesartan but more fatal events, although numbers were very small[53].

• In the **ONTARGET study**, 25,620 patients with atherosclerotic disease or diabetes (38% with diabetes) who had end-organ damage were randomly assigned to treatment with an ACEI, angiotensin receptor blocker (ARB), or both and were followed for a median of 56 months. Although the combination treatment reduced the increase in urinary AER, the number of events for the composite primary outcome or doubling of the serum creatinine level, need for dialysis, or death was similar for telmisartan (N = 1147 [13.4%]) and ramipril (N = 1150 [13.5%]; HR, 1.00; 95% CI, 0.92 to 1.09) but was increased with combination therapy (N = 1233 [14.5%]; HR, 1.09; 95% CI, 1.01 to 1.18; P = 0.037). It is important to stress that the ONTARGET study did not include significant numbers of patients with overt diabetic nephropathy. Therefore, the therapeutic risk or benefit for RAAS combination therapy in patients with diabetic nephropathy could not be addressed by this study [54].

• Patients intolerant to ACE inhibition (n = 5927), but otherwise similar at baseline to patients enrolled in the ONTARGET study, were randomly assigned to receive a placebo or ARB in the **TRANSCEND study**. Albuminuria increased less in patients receiving the ARB than in those receiving placebo (32% [95% CI, 0.23 to 0.41] vs. 63% [95% CI, 0.52 to 0.76]). Very few patients (<2%) reached the prespecified renal end points, which were identical to those of the ONTARGET study, and no difference was seen between treatment groups with regard to these end points [55].

• Parving and co-workers have evaluated the renoprotective effect of the angiotensin II receptor antagonist irbesartan in hypertensive patients with type 2 diabetes and microalbuminuria in the **IRMA 2 trial**. Remission to normoalbuminuria was more common in the irbe-

sartan-treated patients than in those treated with placebo [56].

- The importance of this finding is a slower decrease in GFR, as also demonstrated in the **STENO-2 study** [57].

- The antiproteinuric effect of ACE inhibition in patients with diabetic nephropathy varies considerably. Individual differences in the RAAS may influence this variation. Therefore, the potential role of an ID polymorphism of the ACE gene on this early antiproteinuric responsiveness was tested in an observational follow-up study of young type 1 diabetic patients with hypertension and diabetic nephropathy. The study found that type 1 diabetes patients with the homozygous II genotype were particularly likely to benefit from commonly advocated renoprotective treatment [58].

- The **EUCLID Study** demonstrated that urinary AER during lisinopril treatment was 57% lower in the II group, 19% lower in the ID group, and 19% higher in the DD group compared with the placebo group. Furthermore, the polymorphism of the ACE gene predicts therapeutic efficacy of ACEIs against the progression of nephropathy in type 2 diabetic patients [59].

- In the IDNT, 1715 hypertensive patients with nephropathy (mean serum creatinine 1.7 mg/dL [150 micromol/L]) due to type 2 diabetes were randomly assigned to irbesartan (300 mg/day), amlodipine (10 mg/day), or placebo. At 2.6 years, irbesartan was associated with a risk of the combined endpoint (doubling of the plasma creatinine, development of end-stage renal disease, or death from any cause) that was 23 and 20 percent lower than with amlodipine and placebo, respectively; the values were 37 and 30 percent lower for doubling of the plasma creatinine. These benefits were independent of the differences in the magnitude of blood pressure reduction among the groups, and the renal outcomes were best at systolic pressures below 134 mm Hg [60].

- In the RENAAL trial [61], 1513 patients with type 2 diabetes and nephropathy (mean serum creatinine 1.9 mg/dL [168 micromol/L]) were randomly assigned to losartan (50 titrating up to 100 mg once daily) or placebo, both in addition to conventional antihypertensive therapy (but not ACE inhibitors). Compared to placebo, losartan reduced the incidence of a doubling of the plasma creatinine by 25 percent and end-stage renal disease by 28 percent; the mean follow-up was 3.4 years. These benefits were again not associated with differences in blood pressure levels between the groups. Subsequent analysis of the RENAAL trial found that the most significant risk factor for progressive kidney disease was the degree of proteinuria, both initially and after six months of therapy. Additional post-hoc evaluations of RENAAL revealed the following:

- Every 10 mmHg increase in the baseline systolic blood pressure was associated with an

enhanced risk of end-stage renal disease or death by 6.7 percent.

- Lowering albuminuria within the first six months correlated with a decreased subsequent cardiovascular risk. There was an 18 percent decrease in risk of a cardiovascular event for every 50 percent decrease in the rate of albumin excretion.

- Within all categories of attained blood pressure, a larger reduction in albuminuria correlated with a progressively lower risk of end-stage renal disease.

- The presence of baseline retinopathy was associated with a poor renal outcome (increased proteinuria, decreased GFR, and development of end-stage renal disease) and a higher risk of death.

- However, all these ARB trials were underpowered and of too short duration to detect a possible cardiovascular effect.

- Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial (ORIENT) - 577 type 2 diabetic patients with macroalbuminuria were randomized to the ARB olmesartan or placebo on top of the usual treatment (77% were treated with ACE inhibition). The study found that there was no significant effect on the primary end point—development of ESRD, death, or doubling of the serum creatinine level [62,63].

18. Combination Treatment with ACE Inhibitor and ARB (Dual Therapy)

Cost-effectiveness of early irbesartan treatment versus placebo, in addition to standard conventional blood pressure–lowering treatment, has also been demonstrated. The beneficial effect of RAAS blockade in microalbuminuric patients was also shown in the INNOVATION study in an Asian population [64]. Current evidence suggests that dual therapy is not recommended in diabetic nephropathy. The Veterans Affairs Nephropathy in Diabetes study (VA NEPHRON-D), a randomized placebo-controlled double-blind trial performed in 1448 mostly male patients with diabetic nephropathy (mean estimated GFR [eGFR], 54 mL/min/1.73 m2; mean albumin-to-creatinine ratio, 852 mg/g) showed thatcombination therapy and monotherapy groups had a similar rate of primary events (18.2 versus 21 percent). However, acute kidney injury requiring hospitalization or occurring during hospitalization was significantly more common with dual therapy (18 versus 11 percent), as was severe hyperkalaemia (9.9 versus 4.4 percent) [65]. Additional data from the diabetes subgroup of the ONTARGET trial also suggests similar findings.

19. Aldosterone Antagonists

Spironolactone [65] has been shown to decrease albuminuria and blood pressure in patients with type 1 diabetes. **Eplerenone** [67] may reduce albuminuria in patients with type

2 diabetes. **Finerenone** [68] was evaluated in a phase 2 dose-finding trial of 823 patients with type 2 diabetes treated with an ACE inhibitor or ARB. The effect of seven different doses of finerenone (ranging from 1.25 mg/day to 20 mg/day) was compared with placebo on the change in albuminuria at 90 days. A dose-dependent effect was observed, with albuminuria reductions ranging from 21 to 38 percent with doses ranging from 7.5 mg/day to 20 mg/day. The incidence of hyperkalemia with finerenone treatment was low (1.5 percent); acute reductions in eGFR were mild and were reversible after cessation of the study drug.

19.1. Aliskiren

The use of aliskiren a direct renin inhibitor, in combination with either an ACE inhibitor or ARB does not appear to preserve renal function and increases the risk of adverse events.

This was shown in the multinational Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE trial), which randomly assigned 8561 diabetic patients with either pre-existing renal or cardiovascular disease to 300 mg/day aliskiren or placebo. At baseline, the majority of patients had nephropathy; all patients received an ACE inhibitor or ARB at baseline. After a median follow-up of 32.9 months, adverse events requiring cessation of randomized therapy (usually hyperkalemia) were significantly more frequent with aliskiren (13.2 versus 10.2 percent). Due to the lack of apparent benefit and higher risk of side effects, the trial was stopped early [69].

19.2. Lipid lowering therapy

Study of Heart and Renal Protection (SHARP) investigated the effect of LDL lowering using a combination of simvastatin 20 mg and ezetemibe in 9270 patients with advanced CKD (3023 on dialysis and 6247 not on dialysis). About 20% had diabetes. The treatment reduced the incidence of major atherosclerotic events in a wide range of patients, including diabetic patients, with advanced CKD. There was no effect on mortality [70].

NKF KDOQI recommendations regarding lipid-lowering medications:

- LDL cholesterol-lowering medication (such as statin or statin/ezetimibe combination) recommended for patients with diabetes and chronic kidney disease, including those who have received a kidney transplant.

- Do not start statin therapy in patients with diabetes who are treated by dialysis.

- Atorvastatin might reduce mortality and cardiac events in patients with diabetes on haemodialysis if baseline LDL cholesterol ≥ 145 mg/dL (3.76 mmol/L). This isbased on post hoc subgroup analysis from 4D Study[71]where 1,255 patients with diabetes on haemodialysis were analysed for baseline LDL cholesterol levels. 49% died at median follow-up of 4 years

Atorvastatin was associated with reduced risk in patients with baseline LDL cholesterol ≥ 145 mg/dL (3.76 mmol/L)

Pitavastatin may reduce proteinuria compared to pravastatin in patients with type 2 diabetes and macroalbuminuria. Dose of atorvastatin does not appear to affect progression of nephropathy in patients with type 2 diabetes and early kidney disease (based on randomized trial without clinical outcomes). 119 patients (mean age 64 years) with type 2 diabetes and microalbuminuria or proteinuria were randomized to atorvastatin 80 mg/day vs 10 mg/day and followed for mean 2 years. There was no significant difference in glomerular filtration rate, creatinine clearance, serum creatinine, cystatin C, urine protein or albumin excretion between high- or low-dose atorvastatin. There was no significant difference in death or adverse events either (PANDA trial) [72].

20. Conclusion

Diabetic Nephropathy (DN) is a significant risk for not only developing end stage renal disease but also cardiovascular disease. Natural progression and history of DN is different for type 1 and type 2 diabetes. There are various risk factors for development and progression of DN, some genetic but mostly environmental. They key to halting progression of DN is likely to rest on the 3 key factors of managing **ABC** – strict glycemic control (Hb**A**1C), stringent Blood Pressure (**B**P) targets and achieving adequate **C**holesterol levels.

Specialist clinics and regular monitoring is warranted in managing these patients with DN. There is some good trial evidence with a number of different reno-protective agents for various situations and for specific population groups that may help in DN. However, we still lack specific markers that will detect DN earlier and in a more consistent basis. Also, we still don't have agents to treat DN that will make a significant impact on the long term consequences and improve prognosis for patients with DN.

21. References

1. Prevalence of microalbuminuria and its risk factors in type 2 diabetic patients M. Afkhami-Ardekani, M. Modarresi, E. Amirchaghmaghi: Indian J Nephrol. 2008; 18(3): 112–117.

2. Diagnosis and Classification of Diabetes Mellitus American Diabetes Association Diabetes Care. 2010; 33(Supplement 1): S62-S69.

3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013; 3: 1.

4. Gross JL, de Azevedo MJ, Silveiro SP, et al. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care. 2005; 28:164.

5. Seema Basi, MD, MSCI1, Pierre Fesler, MD2, Albert Mimran, MD2 and Julia B. Lewis, MD3: Microalbuminuria in Type 2 Diabetes and Hypertension A marker, treatment target, or innocent by stander? Diabetes Care. 2008; 31(Supplement 2): S194-S201.

6. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, Ferrario F, Fogo AB, Haas M, de Heer E, Joh K, Noël LH, Radhakrishnan J, Seshan SV, Bajema IM, Bruijn JA; Renal Pathology SocietyPathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010; 21(4): 556-563.

7. Thijs W. Cohen Tervaert, Antien L. Mooyaart, Kerstin Amann, Arthur H. Cohen, H. Terence Cook, Cinthia B. Drachenberg, Franco Ferrario, Agnes B. Fogo, Mark Haas, Emile de Heer, Kensuke Joh, Laure H. Noe¨ l, Jai Radhakrishnan, Surya V. Seshan, Ingeborg M. Bajema, and Jan A. Bruijn, on behalf of the Renal Pathology Society: Pathologic Classification of Diabetic Nephropathy: JASN April 1, 2010 vol. 21 no. 4556-4563.

8. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease Kidney Int Suppl (2011) 2013 Jan; 3(1): 4

9. Genetics of diabetic nephropathy: evidence for major and minor gene effects. AU Krolewski AS SO Kidney Int. 1999; 55(4): 1582.

10. The excess incidence of diabetic end-stage renal disease among blacks. A population-based study of potential explanatory factors.Brancati FL, Whittle JC, Whelton PK, Seidler AJ, Klag MJ JAMA. 1992; 268(21): 3079

11. Incidence of end-stage renal disease in patients with type 1 diabetes:Finne P, Reunanen A, Stenman S, Groop PH, Grönhagen-Riska C: JAMA. 2005; 294(14): 1782.

12. Jeremy W. Tomlinson, Mrcp Katharine R. Owen, Mrcp Colin F. Close, Md:Treating Hypertension in Diabetic Nephropathy.

13. Increased glomerular filtration rate as a predictor of diabetic nephropathy - an 8-year prospective study: Rudberg S, Persson B, Dahlquist G: Kidney Int.1992; 41(4): 822.

14. Wang PH, Lau J, and Chalmers TC: Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. Lancet 1993; 341: pp. 1306-1309

15. Effects of smoking on systemic and intrarenal hemodynamics: influence on renal function:Orth SR: J Am Soc Nephrol. 2004; 15 Suppl 1: S58.

16. Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab):Tapp RJ, Shaw JE, Zimmet PZ, Balkau B, Chadban SJ, Tonkin AM, Welborn TA, Atkins RC Am J Kidney Dis. 2004; 44(5): 792.

17. Oral contraceptives, angiotensin-dependent renal vasoconstriction, and risk of diabetic nephropathy. Ahmed SB, Hovind P, Parving HH, Rossing P, Price DA, Laffel LM, Lansang MC, Stevanovic R, Fisher ND, Hollenberg NK : Diabetes Care. 2005; 28(8): 1988.

18. Hypercholesterolemia -- A determinant of renal function loss and deaths in IDDM patients with nephropathy:Kidney International Supplement. 1994; Issue 45, pS-125-S-131. 7p: Krolewski, Andrzej S; Warram, James H.Christlieb, A. Richard.

19. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64): Richard J. Stevens, Sue E Manley, Rudy W Bilous, Carole A Cull.

20. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus:Thakar CV, Christianson A, Himmelfarb J, Leonard AC:Clin J Am SocNephrol. 2011; 6(11): 2567-2572.

21. J Am Board Fam Med. 2009 Sep-Oct;22(5):521-7. The association of vitamin D deficiency and insufficiency with diabetic nephropathy: implications for health disparities. Diaz VA, Mainous AG 3rd, Carek PJ, Wessell AM, Everett CJ.

22. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II.Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH :Diabetes. 1990;

39(9): 1116.

23. Relationship between retinal and glomerular lesions in IDDM patients. Chavers BM, Mauer SM, Ramsay RC, Steffes MW Diabetes. 1994; 43(3): 441.

24. Clinical predictors of non-diabetic renal disease and role of renal biopsy in diabetic patients with renal involvement: a single centre review.Chong YB, Keng TC, Tan LP, Ng KP, Kong WY, Wong CM, Cheah PL, Looi LM, Tan SY Ren Fail. 2012; 34(3): 323-328.

25. High glucose evokes an intrinsic proapoptotic signaling pathway in mesangial cells.Mishra R, Emancipator SN, Kern T, Simonson MS Kidney Int. 2005; 67(1): 82.

26. The pathogenesis of diabetic nephropathy:Dronavalli, Suma; Duka, Irena; Bakris, George L. Nature Clinical Practice. Endocrinology & Metabolism; London 4.8 2008: 444-452

27. Loss of Tubular Bone Morphogenetic Protein—7 in Diabetic Nephropathy.

28. Regression of Advanced Diabetic Nephropathy by Hepatocyte Growth Factor Gene Therapy in Rat Josep M. Cruzado1, Núria Lloberas2, Joan Torras1, Marta Riera2, Cristina Fillat3, Immaculada Herrero-Fresneda2, Josep M. Aran4, Gabriela Alperovich1, August Vidal5 and Josep M. Grinyó

29. Christensen PK, Larsen S, Horn T, et al: The causes of albuminuria in patients with type 2 diabetes without diabetic retinopathy. Kidney Int 2000; 58: pp. 1719-1731

30. Progressive diabetic nephropathy. How useful is microalbuminuria?: contra Richard J. MacIsaacElif I. Ekinci, G. Jerums.

31. Diabetic Nephropathy:Peter Rossing, Paola Fioretto, Bo Feldt-Rasmussenand Hans-Henrik Parving. InBrenner and Rector's The Kidney, 39, 1283-1321.e14.

32. Reversal of Lesions of Diabetic Nephropathy after Pancreas Transplantation Paola Fioretto, M.D., Ph.D., Michael W. Steffes, M.D., Ph.D., David E.R. Sutherland, M.D., Ph.D., Frederick C. Goetz, M.D., and Michael Mauer, M.D. N Engl J Med.1998; 339: 69-75

33. The SeventhReport of the JointNationalCommittee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.NationalHigh Blood Pressure Education Program. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2004; Report No: 04-5230.

34. Predisposition to Hypertension and Susceptibility to Renal Disease in Insulin-Dependent Diabetes Mellitus. Andrzej S. Krolewski, M.D., Ph.D., MitzyCanessa, Ph.D., James H. Warram, M.D., Lori M.B. Laffel, M.D., Richard Christlieb, M.D., William C. Knowler, M.D., DR.P.H., and Lawrence Rand, M.D.N Engl J Med. 1988; 318: 140-145

35. Myers BD, Nelson RG, Williams GW, et al: Glomerular function in Pima Indians with noninsulin-dependent diabetes mellitus of recent onset. J Clin Invest. 1991; 88: pp. 524-530.

36. In patients with type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. Bruce A. Perkins, Linda H. Ficociello, Bijan Roshan, James H. Warram and Andrzej S. Krolewski.Kidney International 2010; 77: 57–64.

37. Moderately increased albuminuria (microalbuminuria) in type 2 diabetes mellitus. UpToDate - Authors: David K McCulloch, George L Bakris, Section Editors: Richard J Glassock, David M Nathan, Deputy Editor: John P Forman - Nov 11, 2016.

38. National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification Andrew S. Levey, MD; Josef Coresh, MD, PhD; Ethan Balk, MD, MPH; Annamaria T. Kausz, MD, MS; Adeera Levin, MD; Michael W. Steffes, MD, PhD; Ronald J. Hogg, MD; Ronald D. Perrone, MD; Joseph Lau, MD; GarabedEknoyan. Annals of Int Medicine 15 July 2003.

39. Schmitz A, Christensen T, and Jensen FT: Glomerular filtration rate and kidney volume in normoalbuminuric non-insulin-dependent diabetics-lack of glomerular hyperfiltration and renal hypertrophy in uncomplicated NIDDM. Scand J Clin Lab Invest 1989; 49: pp. 103-108

40. Nutrition Recommendations and Interventions for Diabetes. A position statement of the American Diabetes Association. Diabetes Care 2008; 31(Supplement 1): S61-S78.

41. Glycemic Targets - American Diabetes Association.Diabetes Care 2016; 39(Supplement 1): S39-S46.

42. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview by David M. Nathan for the DCCT/EDIC Research Group. Diabetes Care. 2014; 37(1): 9–16.

43. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group.Turner RC1, Cull CA, Frighi V, Holman RR. JAMA. 1999; 281(21): 2005-12.

44. A Summary of the ADVANCE Trial: Simon R. Heller, DM, FRCP and on behalf of the ADVANCE Collaborative Group : Diabetes Care. 2009; 32(Suppl 2): S357–S361.

45. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. William Duckworth, Carlos Abraira, Thomas Moritz, et al. for the VADT Investigators. N Engl J Med .2009; 360: 129-139.

46. Monami M, Dicembrini I, Martelli D, et al. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. Curr Med Res Opin. 2011; 27: 57–64.

47. Effects of once-weekly dulaglutide on kidney function in patients with type 2 diabetes in phase II and III clinical trials. Katherine R. Tuttle, T. Dwight McKinney, Jaime A. Davidson, Greg Anglin, Kristine D. Harper, Fady T. Botros. Diabetes, Obesity & Metabolism: 24 November 2016.

48. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators. N Engl J Med. 2015; 373: 2117-2128.

49. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311(5): 507-520.

50. The Canadian Society of Nephrology 2014 Clinical Practice Guideline for management of blood pressure in CKD - AJKD 2014; 63: 869-887.

51. Bilous R1, Chaturvedi N, Sjølie AK, Fuller J, Klein R, Orchard T, Porta M, Parving HH. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. Ann Intern Med. 2009; 151(1): 11-20.

52. Preventing Microalbuminuria in Type 2 Diabetes. Piero Ruggenenti, M.D., Anna Fassi, M.D., AneljaParvanovaIlieva et al, for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. N Engl J Med. 2004; 351:1941-1951.

53. Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes. Hermann Haller, M.D., Sadayoshi Ito, M.D., Ph.D., Joseph L. Izzo, Jr., M.D., Andrzej Januszewicz et al, for the ROADMAP Trial Investigators. N Engl J Med. 2011; 364: 907-917.

54. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events: The ONTARGET Investigators. N Engl J Med. 2008; 358: 1547-1559.

55. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. The Telmisartan Randomised AssessmeNt

Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Lancet 2008; 372: p1174–1183.

56. Prevention and Treatment of Diabetic Nephropathy: The Program for Irbesartan Mortality and Morbidity EvaluationDr. Giacomo Deferrari, Department of Internal Medicine, Viale Benedetto XV, 6-16123

57. Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes. Peter Gæde, Henrik Lund-Andersen, Hans-Henrik Parving, and Oluf Pedersen: N Engl J Med. 2008; 358:580-589.

58. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels.BRigat, C Hubert, F Alhenc-Gelas, F Cambien, P Corvol, and F Soubrier : J Clin Invest. 1990; 86(4): 1343–1346.

59. The EUCLID Study Group writers. “Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria”. The Lancet. 1997; 349(9068): 1787-1792.

60. Lewis EJ, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. The New England Journal of Medicine. 2001; 345(12): 851-860.

61. Brenner BM, et al. “Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy”. The New England Journal of Medicine. 2001; 345(12): 861-869.

62. ORIENT: Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy: Imai E, Haneda M, Chan JC, Yamasaki T, Kobayashi F, Ito S, Makino H. Reduction and residual proteinuria are therapeutic targets in type 2 diabetes with overt nephropathy: a post hoc analysis (ORIENT-proteinuria). Nephrol Dial Transplant. 2013; 28(10): 2526-2534.

63. Imai E, Chan JC, Ito S, Yamasaki T, Kobayashi F, Haneda M, Makino H; ORIENT study investigators. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. Diabetologia. 2011; 54(12): 2978-2986.

64. A Randomised, Double-blind, Placebo-controlled, Multicenter Trial to Investigate the Preventive Effect of BIBR277 (Telmisartan) in Diabetic Nephropathy on Transition From Incipient to Overt Nephropathy - Incipient to Overt: Angiotensin 2 Receptor Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION Study).

65. VA NEPHRON-D: Diabetes iN Nephropathy Study (VA NEPHRON-D). Clinical Trials.gov Identifier: NCT00555217.

66. Rachmani R, Slavachevski I, Amit M et al. The effect of spironolactone, cilazapril and the combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: A randomised controlled study. Diabet Med. 2004; 21: 471-475.

67. Eptein, M, Williams GH, Weinberger M et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol. 2006; 1: 940-951.

68. Bakris GL, Agarwal R, Chan JC, Cooper ME et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy – for mineralocorticoid receptor antagonist tolerability study – diabetic nephropathy – ARTS-DN study group. JAMA. 2015; 314(9): 884-894

69. Parving HH, Brenner BM, McMurridge AJ et al. Aliskiren trial in type 2 diabetes using cardiorenal end-points (ALTITUDE): Rationale and study design. Nephrol Dial Transplant. 2009; 24: 1663-1671.

70. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Colin Baigent, Martin J Landray, Christina Reith, Jonathan Emberson, David C Wheeler et al, on behalf of the SHARP Investigators Lancet. 2011; 377: 2181–92.

71. Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis. Christoph Wanner, M.D., Vera Krane, M.D., Winfried März, M.D., Manfred Olschewski, M.Sc., Johannes F.E. Mann, M.D., Günther Ruf, M.D., and

Eberhard Ritz, M.D., for the German Diabetes and Dialysis Study Investigators N Engl J Med. 2005; 353: 238-248.

72. Protection Against Nephropathy in Diabetes with Atorvastatin (PANDA): a randomized double-blind placebo-controlled trial of high- vs. low-dose atorvastatin.Rutter MK1, Prais HR, Charlton-Menys V, Gittins M, Roberts C, Davies RR, Moorhouse A, Jinadev P, France M, Wiles PG, Gibson JM, Dean J, Kalra PA, Cruickshank JK, Durrington PN. Diabet Med. 2011; 28 (1): 100-108.