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Diabetes Mellitus Type 2 and Proteinuria

Relu Cernes and Reuven Zimlichman

Additional information is available at the end of the chapter

1. Introduction

Worldwide the prevalence of diabetes was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [1]. The spread will be higher in developing countries (69%) compared to developed countries (20%). Most of diabetic patients will have type 2 diabetes [2].

Chronic kidney disease (CKD) is prevalent in people with diabetes; a recent analysis of NHANES data found that 39.6% of people with diagnosed diabetes, 41.7% of those with undiagnosed diabetes and 17.7% of those with prediabetes had CKD [3]. Increased urinary protein excretion may be an early clinical manifestation of diabetic nephropathy. However, when assessing protein excretion, the urine dipstick is a relatively insensitive marker for initial increases in protein excretion, not becoming positive until protein excretion exceeds 300 to 500 mg/day (upper limit of normal less than 150 mg/day, with most individuals excreting less than 100 mg/day) [4]. Microalbuminuria is delimited as an albumin excretion rate of 30-300 mg/24 h or a spot urine albumin to creatinine Ratio (ACR) of 30-300 mg/g (3.5-35 mg/mmol) in males and 20-200 mg/g (2.5-25 mg/mmol) in females. Overt diabetic nephropathy (DN) is settled by proteinuria >500 mg/24 h or albuminuria >300 mg/24 h. Also DN can be defined by an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 [5]. 5097 subjects with type 2 diabetes were followed from 1977 to 1997 to determine the rate of progression of kidney disease. From diagnosis of diabetes, progression to microalbuminuria occurred at 2.0% per year, from microalbuminuria to macroalbuminuria at 2.8% per year, and from macroalbuminuria to elevated plasma creatinine (>or=175 micromol/L) or renal replacement therapy (RRT) at 2.3% per year. Ten years following diagnosis of diabetes, the prevalence of microalbuminuria was 24.9%, of macroalbuminuria was 5.3%, and of elevated plasma creatinine or RRT was 0.8% [6]. Renal dysfunction, including proteinuria and microalbuminuria, is predictive of cardiovascular events, and cardiovascular and all-cause mortality [7-11]. Although these cutoffs defining normoalbuminuria, microalbuminuria, and macroalbuminuria facilitate deter-

mining the risk for progression of nephropathy, the risk of developing overt diabetic nephropathy is probably directly related to albumin excretion rates at all levels. A recent collaborative meta-analysis of general population cohorts involving more than 1 million participants has provided strong evidence of the direct relationship between renal dysfunction and cardiovascular risk [12]. eGFR < 60 ml/min/1.73 m 2 and (ACR) 1.1 mg/mmol (10 mg/g) were both independent predictors of mortality risk in the general population. The two parameters increased mortality in a multiplicative fashion, without evidence of interaction [12]. The clinical significance, screening, prevention and management of proteinuria in patients with type 2 diabetes will be reviewed here.

Mortality rates for those with nephropathy are high, increasing from 1.4% per year in nor-moalbuminuria to 4.6% per year (clinical grade proteinuria), and to 19.2% per year those with renal impairment. More intensive blood glucose control resulted in both a 33% reduction in relative risk of development of microalbuminuria or clinical grade proteinuria at 12 years, and a significant reduction in the proportion doubling their plasma creatinine (0.91 vs. 3.52%, P = 0.0028). These data underline the importance of glycaemic and blood pressure control in type 2 diabetes in order to prevent diabetic nephropathy [13]. Asian and hispanic patients with type 2 diabetes had a high prevalence of proteinuria and reduced kidney function [14,15]. In Caucasian non-insulin dependent diabetic baseline microalbuminuria, male gender, presence of retinopathy, S-cholesterol, HbA1c, and age was found to predict the development of incipient/overt diabetic nephropathy [16]. To estimate the frequency of remission/regression of microalbuminuria and to identify factors affecting such outcomes 216 Japanese patients with type 2 diabetes and microalbuminuria were enrolled and observed during an initial 2-year evaluation period. Remission was defined as shift to normoalbuminuria and regression as a 50% reduction in urinary albumin excretion rate (UAER)from one 2-year period to the next. Reduction of urinary UAER was frequent, with a 6-year cumulative incidence of 51% (95% CI 42-60) for remission and 54% for regression, whereas the frequency of progression to overt proteinuria was 28%. Microalbuminuria of short duration, the use of renin-angiotensin system-blocking drugs, and lower tertiles for HbA(1c) (<6.95%) and systolic blood pressure (<129 mmHg) were independently associated with remission or regression in the pooled logistic regression analysis. Early detection of microalbuminuria and a multifactorial control may result in improved outcomes for diabetic nephropathy and cardiovascular events [17].

2. Pathogenesis

Microalbuminuria and macroalbuminuria are not only markers of nephropathy but also causes of disease progression. Proteinuria may accelerate kidney disease progression to end-stage renal failure through multiple pathways, including induction of tubular chemokine expression and complement activation that lead to inflammatory cell infiltration in the interstitium and sustained fibrogenesis [18]. The precise mechanisms by which albumin leaves the bloodstream, crosses the endothelial suface layer, glomerural endothelial fenestrae, the glomerural base-ment membrane, the sleet pores between the foot processes of the podocytes and the subpo-

docyte space and by which albumin passes through Bowman's space and the tubuli and at the end enters into the urine remain an area of research and debate [19].

Glomerular hemodynamics and renin-angiotensin system (RAS). Proteinuria may be detected in healthy people after sustained exercise. Unbalance between afferent artery and efferent artery may appear during vigorous physical effort. Renal blood flow decreases and GFR is maintained by increment in intraglomerural pressure. Intraglomerural hypertension induces albuminuria. Also in DN, albuminuria is induced by a reduction in renal mass. Preserved glomeruli compensate the sclerotic ones by dilatation of afferent arterioles, constriction of efferent arterioles, increment of intraglomerural hydrostatic pressure. When this process continues, the glomerular barrier is compromised and albumin enters into the urine [20]. Leak of albumin into the urine is partly blocked by RAS inhibition also in healthy subjects [21]. RAS plays a central role as a mediator of glomerural hemodynamic and injury. Therapeutic blockade of RAS slows the disease progression not only by hemodynamic action but also by induction of profibrotic agents. Angiotensin II (Ang II) also plays an important role in glomerulosclerosis through induction of transforming growth factor –β (TGF- β) expression in mesangial cell [22]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can attenuate progressive glomerulosclerosis without altering glomerular pressures. Because agents that interfere with Ang II action may decrease glomerular injury, it has been suggested that Ang II has direct effects on glomerular cells to induce sclerosis independent of its hemodynamic actions.Antagonizing the profibrotic effects of angiotensin II may also be a significant factor in benefits observed with ACE inhibitors and ARBS [22].

3. Endothelial barrier and glomerural basement membrane

The endothelium of glomerural capillaries is fenestrated. The diameter of endothelial pores is 60-100 nm. Although the albumin diameter is smaller than the pore diameter (8nm) the endothelium is not working like a sieve [24]. A glycoprotein coat covers capillary endothelium like a gel-like diaphragm. Damage of diaphragm in diabetic patients is associated with proteinuria [25].

The glomerural basement membrane was considered a mechanical and electrostatic barrier. The loss negatively charged proteoglycans is associated with albumin cross. Today,the mechanical role of glomerural basement membrane is less important [14,26]. Although the glomerural basement membrane is thick in diabetic patients, the leakage of albumin is increased [26].

4. Podocytes

Podocytes are highly specialized cells of the kidney glomerulus that help to prevent proteinuria through regulation of the actin cytoskeleton in their foot processes. Podocytopenia

correlates with disease progression and is related inversely to the control of hypertension and diabetes. Diabetes mellitus induces podocytopenia through several mechanisms.

Podocyte morphological changes in DN are flattening and retraction. Podocyte dysfunction reduces ultrafiltration and induces intraglomerural hypertension and proteinuria. Podocytes are detected in the urine of diabetic patients and proves that this type of cells are in a proliferation apoptosis cycle [27].

Defects in podocyte-specific insulin signaling may contribute to diabetic nephropathy. Two mouse models have been engineered in which the gene encoding the insulin receptor from the podocyte is deleted [28]. In the absence of hyperglycemia, affected mice develop albuminuria, effacement of foot processes, apoptosis, glomerular basement membrane thickening, accumulation of mesangial matrix and glomerulosclerosis. Activation of the insulin receptor appears to trigger remodeling of the actin cytoskeleton through the mitogen-activated protein kinase 42/44 (MAPK) and phosphatidylinositol 3 (PI3) kinase signaling pathways, suggesting a possible mechanism of proteinuria. The podocyte insulin receptor is an attractive target for agents that prevent proteinuria and development and progression of diabetic nephropathy [29].

Podocytes are linked by a porous diaphragm with pores diameter of 12 nm. The integrity of the diaphragm has a great importance in prevention of proteinuria, Several diaphragm protein mutations like nephrin and podocin are associated with nephritic syndrome. When compared with nondiabetic patients with minimal change nephropathy and controls, patients with diabetic nephropathy had a downregulation of nephrin expression and fewer electron dense slit diaphragms [30].

5. Bowman 's space and proximal tubule

Bowman's space is situated between the parietal layer of Bowman's capsule and podocytes. Bowman's space is important in ultrafiltration and hydraulic resistance. The hydrostatic pressure is reduced in diabetic patients and appears to be associates with albuminuria [31]. Tubules suffer a number of structural and functional changes in DN. Tubules are hypertrophic and tubular basement membrane is thickened before proteinuria appearance. Tubular filtration is impaired through several mechanisms: lysosomal dysfunction; albumin transporters' reduction like megalin and cubilin; apical brush border changes and cathepsin-mediated proteolytic activity decrease [32,33].

Advanced Glycation End Products (AGEs) AGEs are the product of nonenzymatic reaction between the aldehyde group of sugars and carbonyls of proteins, lipids and nucleic acids. The first stable product is Amadori complex like HBA1c [34]. AGEs induce mesangial expansion and injury, through activation of AGE receptors (RAGE) perhaps in part via increased matrix production or glycation of matrix proteins [34]. The potential significance of RAGE in diabetic kidney is demonstrated by prevention of indices of mesangial expansion, thickening of the glomerural basement membrane and reduced albuminuria in RAGE knockout (KO) mice and following intervention with RAGE antibodies; on the other hand RAGE activation may

produce renal damage [35,36]. The net effect is tissue accumulation of AGEs, in part by crosslinking with collagen, which can contribute to the associated renal and microvascular complications [37].

Prorenin — Renin is an aspartyl-protease that exists in two forms, the proenzyme prorenin and mature renin. Prorenin is transformed into mature renin by cleavage of the 43 amino acids of the pro-segment. Prorenin, although synthesized by a restricted number of tissues, represents up to 90% of total plasma renin in normal subjects. Experimental data on transgenic rats confirm a link between the overexpression of the receptor and cardiovascular and renal dysfunctions possibly involving direct activation of the receptor by (pro)renin [38]. Prorenin receptor blockade with a short peptide of prorenin practically abolished the increased mitogen-activated protein kinase (MAPK) activation and nephropathy despite unaltered increase in AngII in diabetic kidney. These results indicate that the MAPK activation signal leads to the diabetic nephropathy but not other renin-angiotensin system-activated mechanisms in the glomeruli. It is not only AngII but also intraglomerular activation of MAPK by the receptor-associated prorenin that plays a pivotal role in diabetic nephropathy [39].

Cytokines — Angiogenetic factors may explain pathologic changes in DN. Vascular endothelial growth factor (VEGF) is one of the main angiogenetic factors. Its expression and signaling in the kidney are amplified early on in the diabetic state. Moreover, counteracting its effects reverses the albuminuria and other hemodynamic and structural features of experimental DN. Finally, experimental overexpression of VEGF in adult mice replicates several aspects of diabetic kidney disease [41]. Under the influence of a variety of diabetic mediators, the podocyte becomes the main source of increased expression of VEGF in the kidney. The cytokine then exerts its multitude of effects in an autocrine fashion on the podocyte itself, on the endothelial cell in a paracrine manner, and finally contributes to macrophage recruitment acting as a chemokine [41,42]. The angiopoietins consist primarily of two main factors acting in contrast to each other: Ang I--an antiangiogenic ligand, and Ang II--its competitive inhibitor. Both, however, seem to have important roles in the maintenance of glomerular homeostasis [43]. Diabetes disrupts the tight balance that controls angiopoietin expression and function and decreases theAngI/AngII ratio. The end physiologic result seems to be dependent on the concomitant VEGF changes in the kidney. Because of the intricacy of their control, angiogenic factors are difficult to manipulate therapeutically [41,43].

TGF- β is a key factor in the development of diabetic complications by activating downstream mediators called Smad2 and Smad3. Hyperglycemia can induce TGF- β and Smads stimulation and renal fibrosis through MAPK and NF-kB pathways [44]

6. Detection and screening

Establishing the diagnosis of microalbuminuria requires the demonstration of an elevation in albumin excretion (30 to 300 mg/day). An elevated ratio should be confirmed with at least two additional tests performed over the subsequent three to six months, with confirmation of the diagnosis requiring at least two of three positive samples [45]. Patients with diabetes mellitus

type 2 must be screened annually, starting at diagnosis. Fever, exercise, heart failure, and poor glycemic control are among the factors that can cause transient microalbuminuria [46]. There are many methods to screen for abnormal amounts of proteinuria to identify patients at risk for progression of renal disease. 701 patients with type 2 diabetes and nephropathy partici-pating in the Reduction of Endpoints in Non Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial were enrolled to compare the ability of urinary protein excretion (UPE) and urinary albumin excretion (UAE) from a 24-hour urine collection and urinary albumin concentration (UAC) and the albumin:creatinine ratio (ACR) from a first-morning void in predicting renal events. The primary outcome measure was the time to a doubling of serum creatinine or end-stage renal disease. During follow-up, 202 events occurred. The hazard ratios for the risk of a renal outcome (95% CIs) associated with 1-SD increment in the log-transformed measures were 3.16 (2.60 to 3.86) for UAE, 3.02 (2.53 to 3.62) for UPE, 3.23 (2.67 to 3.91) for UAC, and 4.36 (3.50 to 5.45) for ACR. The area under the ROC curve was significantly higher for ACR compared with the other measures. In conclusion, measurement of the albumin:creatinine ratio in a first-morning void is the superior method to predict renal events in patients with type 2 diabetes and nephropathy,but the difference compared to spot urine samples at other times was not significant [46,47]. The recommended albumin (microg)/creatinine (mg) ratio (ACR) (30 microg/mg) to detect microalbuminuria does not account for sex or racial differences in creatinine excretion. Mean urine albumin concen-tration were not significantly different between men and women, but urine creatinine concentrations is significantly higher. No significant difference in the prevalence of microal-buminuria between men and women was noted when sex-specific ACR cutpoints are used (> or =17 microg/mg in men and > or =25 microg/mg in women). The use of one ACR value to define microalbuminuria may underestimate microalbuminuria in subjects with higher muscle mass (men) and possibly members of certain racial/ethnic groups [48]. The most pronounced benefits of glycaemic control are on retinal and renal complications in both normoalbuminuric and microalbuminuric patients considered together, with little or no evidence of any greater benefit in those with microalbuminuria. Hence, microalbuminuric status may be a false boundary when considering the benefits of glycaemic control. Classifi-cation of a person as normoalbuminuric must not serve to suggest that they will derive less benefit from optimal glycaemic control than a person who is microalbuminuric. All hyperten-sive patients benefit from blood pressure lowering [49].

7. Treatment and prevention

Glycemic and blood pressure control, particularly with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), have shown to reduce proteinuria, preserve renal function in diabetic patients and reduce cardiovascular events [50].

Lifestyle improvement is the first step in the treatment of DN. This includes a number of measures: avoidance or cessation of smoking, weight reduction and maintaining body mass index (BMI) between 18.5 and 24.9; physical activity, especially regular aerobic physical activity such as brisk walking for more than 30 minutes per day, most days of the week; low

protein diet and reducing protein intake to 0.8-1.0 g/kg body weight per day, most days of the week; low sodium intake to less than 100 mmol /d (2.4 g of sodium or 6 g of sodium chloride) consuming a diet rich in fruits, vegetables, and low fat diary products (DASH diet); low alcohol intake, not more than two drinks for men and one drink for women). For patients with diabetes, clinical practice guidelines recommend treating to a low-density lipoprotein cholesterol (LDL-C) goal of < 100 mg/dL and <70 mg/dl for very high risk patients, using statins as first line treatment [46,51].

8. Blood pressure control and renin-angiotensin blockade

All current guidelines recommend a blood pressure goal in patients with diabetes <130 ⁄ 80 mm Hg. The proportion of diabetic individuals taking lipid- and BP-lowering agents has increased significantly in recent years. However, while there has been a significant improvement in LDL-C goal attainment, nearly one-half of all U.S. adults with diabetes are not at recommended LDL-C or BP treatment goals [52]. Patients with HTN and diabetes have a 7-fold greater risk for progressing to end-stage renal disease (ESRD) and 2 to 4-fold greater risk of developing cardiovascular disease. The first lone treatment are ACEI and ARBS due to renoprotective effect [53,54]. If the baseline BP is >150 ⁄ 90 mm Hg, a second agent should be added, preferably a thiazide diuretic, because they can add cardiovascular protection [54,55]. However, recent evidence suggests that calcium channel blockers, especially amlodipine can comparatively reduce cardiovascular events [56].

Several clinical trials have proved evidence that the conventional treatments for renoprotection including blood pressure regulation, tight glucose control, renin-angiotensin system inhibition, lifestyle modifications and medical team improvement reduce the morbidity and mortality associated with proteinuria. The benefit of ACEI and ARBS in reducing proteinuria and renal preservation in DN has been confirmed in several large randomized trials. Some of them are summarized in Table 1 and detailed in this paragraph.

9. ACEI

In a randomized, double-blind, placebo-controlled trial 94 patients with normal blood pressure and microalbuminuria were assigned to receive enalapril, 10 mg per day, or placebo. After 5 years albuminuria decreased from 143 +/- 64 (mg/24 h to 122 +/- 67 mg/24 h during the first year. In the placebo group microalbuminuria slowly increased to 140 +/- 134 mg/24 [P<0.05]). Kidney function (expressed as mean reciprocal creatinine) declined by 13% in the placebo group and remained stable (-1%) in the enalapril group (P<0.05) [57]. Later this study was done on diabetic patients with normal blood pressure and normoalbuminuria. In a randomized, double-blind, placebo-controlled trial, 156 patients were assigned to receive enalapril, 10 mg/d, or placebo for a period of 6 years. Enalapril therapy decreased albumin excretion from 11.6 +/- 7 mg/24 h to 9.7 +/- 6 mg/24 h at 2 years. This was followed by a gradual increase to 15.8 +/- 8 mg/24 h at 6

years. In the placebo group, albumin excretion increased from 10.8 +/- 8 mg/24 h to 26.5 +/- 10 mg/24 h at 6 years (P = 0.001 for enalapril compared with placebo). Transition to microalbuminuria occurred in 15 of 79 (19%) placebo recipients and 5 of 77 (6.5%) enalapril recipients. Enalapril treatment resulted in an absolute risk reduction of 12.5% (95% CI, 2% to 23%; P = 0.042) for development of microalbuminuria. After 6 years, creatinine clearance decreased from 1.78 +/- 0.13 mL/s to 1.63 +/- 0.12 mL/s (mean decrease, 0.025 mL/s per year) in enalapril recipients and from 1.81 +/- 0.15 mL/s to 1.57 +/- 0.17 mL/s (mean decrease, 0.04 mL/s per year) in placebo recipients (P = 0.040) [58].

10. ARBS

In IRMA-2 (Irbesartan Microalbuminuria in Hypertensive Patients with Type 2 Diabetes),the renoprotective effect of the angiotensin-II-receptor antagonist irbesartan independently of its blood-pressure-lowering effect was evaluated in hypertensive patients with type 2 diabetes and microalbuminuria. 590 patients were enrolled in a randomized, double-blind, placebo-controlled study of irbesartan, at a dose of either 150 mg daily or 300 mg daily, and were followed for two years. The primary outcome was the time to the onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens, with a urinary albumin excretion rate that was greater than 200 ucg per minute and at least 30 percent higher than the base-line level. Ten of the 194 patients in the 300-mg group (5.2 percent) and 19 of the 195 patients in the 150-mg group (9.7 percent) reached the primary end point, as compared with 30 of the 201 patients in the placebo group (14.9 percent) (hazard ratios, 0.30 [95 percent confidence interval, 0.14 to 0.61; P<0.001]and 0.61 [95 percent confidence interval, 0.34 to 1.08; P=0.081 for the two irbesartan groups, respectively) [59]. The Angiotensin II Antagonist Losartan (RENAAL) study investigated renoprotective role of albuminuria reduction in 1428 patients with hypertension and diabetic nephropathy from the placebo-controlled Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study. Among patients with a reduced blood pressure during treatment, a lack of albuminuria reduction was observed in 37, 26, and 51% (total, losartan, and placebo, respectively) at month 6. Blood pressure or albuminuria reduction was associated with a lower risk for end stage renal failure, whereas combined blood pressure and albuminuria reduction was associated with the lowest risk for events [60]. The MicroAlbuminuria Reduction With VALsartan (MARVAL) study investigated the BP-independent effect of valsartan to reduce microalbuminuria in type 2 diabetic patients. Three hundred thirty-two patients with type 2 diabetes and microalbuminuria, with or without hypertension, were randomly assigned to 80 mg/d valsartan or 5 mg/d amlodipine for 24 weeks. The primary end point was the percent change in UAER from baseline to 24 weeks. The UAER at 24 weeks was 56% (95% CI, 49.6 to 63.0) of baseline with valsartan and 92% (95% CI, 81.7 to 103.7) of baseline with amlodipine, a highly significant between-group effect (P<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive subgroups. More patients reversed to normoalbuminuria with valsartan (29.9% versus 14.5%; P=0.001)., valsartan lowered UAER more effectively than amlodipine in patients with type 2 diabetes and microalbuminuria, including the subgroup with baseline

normotension [61]. In ROADMAP trial olmesartan was associated with a delayed onset of microalbuminuria, even though blood-pressure control in both groups was excellent according to current standards [62]. Although in other studies ARBS were effective in reducing cardio-vascular morbidity and mortality as well as mortality from all causes in patients with hypertension, diabetes, and left ventricular hypertrophy, in ROADMAP study the higher rate of fatal cardiovascular events with olmesartan among patients with preexisting coronary heart disease is of concern [62,63]. Several trials do not permit a conclusion about the efficacy of angiotensin inhibition for the prevention of new onset microalbuminuria in normotensive patients with type 2 diabetes. The DIRECT (Diabetic Retinopathy Candesartan Trials) Program are three randomized studies. 3326 and 1905 patients with type 1 and type 2 diabetes, respectively, most were normotensive, and all had normoalbuminuria (median urinary albumin excretion rate, 5.0 microg/min) were assigned to receive candesartan, 16 mg/d increasing to 32 mg/d, versus placebo, for a period of 4.7 years. The primary end point was new microalbuminuria (3 or 4 collections of urinary albumin excretion rate>or=20 microg/min). Individual and pooled results of the 3 trials showed that candesartan had little effect on risk for microalbuminuria (pooled hazard ratio, 0.95 [95% CI, 0.78 to 1.16]; P = 0.60). Pooled results showed that the annual rate of change in albuminuria was 5.53% lower (CI, 0.73% to 10.14%; P = 0.024) with candesartan than with placebo. Candesartan, 32 mg/d, for 4.7 years did not prevent microalbuminuria in mainly normotensive patients with type 1 or type 2 diabetes [64]. The normotensive Appropriate Blood pressure Control in Diabetes (ABCD) trial study investigated the effect of intensive versus moderate diastolic blood pressure (DBP) control on diabetic vascular complications in 480 normotensive type 2 diabetic patients. 480 patients randomized to intensive (10 mm Hg below the baseline DBP) versus moderate (80 to 89 mm Hg) DBP control. Patients in the moderate therapy group were given placebo, while the patients randomized to intensive therapy received either nisoldipine or enalapril in a blinded manner for 5.3 years. The primary end point evaluated was the change in creatinine clearance with the secondary endpoints consisting of change in urinary albumin excretion, progression of retinopathy and neuropathy and the incidence of cardiovascular disease. Mean BP in the intensive group was 128 +/- 0.8/75 +/- 0.3 mm Hg versus 137 +/- 0.7/81 +/- 0.3 mm Hg in the moderate group, P<0.0001. Although no difference was demonstrated in creatinine clearance (P = 0.43), a lower percentage of patients in the intensive group progressed from normoalbuminuria to microalbuminuria (P = 0.012) and microalbuminuria to overt albuminuria (P = 0.028). The intensive BP control group also demonstrated less progression of diabetic retinopathy (P = 0.019) and a lower incidence of strokes (P = 0.03). The results were the same whether enalapril or nisoldipine was used as the initial antihypertensive agent [65].

11. ACEI and ARBS

A number of trials were designed to address the lack of comparative data on the long-term effects of ARBS versus ACEI on renoprotection. The Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) trial is a randomized comparative of these agents. 250 patients with type 2 diabetes and early nephropathy as defined by albuminuria (82 percent microalbuminuria

and 18 percent macroalbuminuria to a maximum of 1.4 g/day) and a baseline GFR (measured isotopically) of approximately 93 mL/min per 1.73 m2 patients were assigned to receive an ACEI, enalapril to an ARB,telmisartan. A greater fall in GFR of at least 10.0 mL/min per 1.73 m2 at five years was predefined as suggesting a clinically significant difference between the two treatment groups.At five years, there was a smaller decline in GFR with enalapril that was not significant (14.9 versus 17.9 mL/min per 1.73 m2 with telnmisartan). Both groups had similar rates or findings for the secondary end points, which included annual changes in the GFR, blood pressure, serum creatinine concentration, urinary albumin excretion, end-stage kidney disease, cardiovascular events, and mortality [66]. In the candesartan and lisinopril microalbuminuria (CALM) study was assessed and compared the effects of candesartan or lisinopril, or both, on blood pressure and urinary albumin excretion in patients with microal-buminuria, hypertension, and type 2 diabetes. Candesartan 16 mg once daily, lisinopril 20 mg once daily were administered to 199 patients in a prospective, randomised, parallel group, double blind study.It run in period and 12 weeks' monotherapy with candesartan or lisinopril followed by 12 weeks' monotherapy or combination treatment. the reduction in urinary albumin:creatinine ratio with combination treatment (50%, 36% to 61%, P<0.001) was greater than with candesartan (24%, 0% to 43%, P=0.05) and lisinopril (39%, 20% to 54%, P<0.001) [67]. In other trials the benefit of combination therapy of ACEI along with ARB reduce proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes [68]. The ONTARGET study investigated the renal effects of ramipril (an ACE inhibitor), telmisartan (an ARB), and their combination in patients aged 55 years or older with established athero-sclerotic vascular disease or with diabetes with end-organ damage. The trial ran for six years. After a 3-week run-in period, 25 620 participants were randomly assigned to ramipril 10 mg a day (n=8576), telmisartan 80 mg a day (n=8542), or to a combination of both drugs (n=8502; median follow-up was 56 months), and renal function and proteinuria were measured. The primary renal outcome was a composite of dialysis, doubling of serum creatinine, and death. The number of events for the composite primary outcome was similar for telmisartan (n=1147 [13.4%]) and ramipril (1150 [13.5%]; hazard ratio [HR] 1.00, 95% CI 0.92-1.09), but was increased with combination therapy (1233 [14.5%]; HR 1.09, 1.01-1.18, p=0.037). The secondary renal outcome, dialysis or doubling of serum creatinine, was similar with telmisartan (189 [2.21%]) and ramipril (174 [2.03%]; HR 1.09, 0.89-1.34) and more frequent with combination therapy (212 [2.49%]: HR 1.24, 1.01-1.51, p=0.038). Estimated glomerular filtration rate (eGFR) declined least with ramipril compared with telmisartan (-2.82 [SD 17.2] mL/min/1.73 m(2)vs -4.12 [17.4], p<0.0001) or combination therapy (-6.11 [17.9], p<0.0001). The increase in urinary albumin excretion was less with telmisartan (p=0.004) or with combination therapy (p=0.001) than with ramipril [68]. The ORIENT study examined the effects of olmesartan, an ARB, on primary composite outcome of doubling of serum creatinine, endstage renal disease and death in type 2 diabetic patients with overt nephropathy [69]. Secondary outcome included composite cardiovascular outcomes, changes in renal function and proteinuria. Five hundred and seventy-seven (377 Japanese, 200 Chinese) patients treated with antihypertensive therapy (73.5%) received concomitant ACEI), were given either once-daily olmesartan (10-40 mg) or placebo over 3.2 years (In the olmesartan group, 116 developed the primary outcome (41.1%) compared with 129 (45.4%) in the placebo group (HR 0.97, 95% CI 0.75, 1.24; p=0.791). Olme-

sartan significantly decreased blood pressure, proteinuria and rate of change of reciprocal serum creatinine. Cardiovascular death was higher in the olmesartan group than the placebo group (ten vs three cases), whereas major adverse cardiovascular events (cardiovascular death plus non-fatal stroke and myocardial infarction) and all-cause death were similar between the two groups (major adverse cardiovascular events 18 vs 21 cases, all-cause deaths; 19 vs 20 cases). Hyperkalaemia was more frequent in the olmesartan group than the placebo group (9.2% vs 5.3%) [69]. The benefit of the combined use of a renin-angiotensin system inhibitor with other antihypertensive drugs such as diuretics or nondihydropyridine calcium channel blockers was studied.

12. Aliskiren, spironolactone and others

The ADVANCE trial investigated if controlling the blood pressure with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy reduces the risks of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease.

Study	Patient population and duration	Treatment	Primary endpoint	Benefit and outcomes
Ravid (1993) [57]	Normotensive+microalbuminuria (5 years)	Enalapril vs placebo	Microalbuminuria reduction	Confirmed
Ravid (1998) [58]	Normotensive+normoalbuminuria (6 years)	Enalapril vs placebo	Albuminuria prevention	Confirmed
IRMA-2 [59]	Hypertension+microalbuminuria (2 years)	Irbesartan vs placebo	Albuminuria reduction	Confirmed, independently of BP
RENAAL [60]	Hypertension+microalbuminuria (6 months)	Losartan vs placebo	Albuminuria reduction	Confirmed, independently of BP
MARVAL [61]	Hypertension(or normotensive) +microalbuminuria (24 weeks)	Valsartan vs placebo	Albuminuria reduction	Confirmed, independently of BP
ROADMAP [62]	Hypertension +normoalbuminuria (3.2 years)	Olmesartan vs. placebo	Albuminuria prevention	Confirmed Higher fatal CV events
ABCD [65]	Hyper or normotension without overt DN (5 years)	Intensive / standard BP treatment	Overt DN prevention and reduction	Overt DN can not be reversed
DIRECT [64]	Normotensive+normoalbuminuria (4.7 years)	Candesartan vs placebo	Albuminuria prevention	Did not prevent microalbuminuria

Study	Patient population and duration	Treatment	Primary endpoint	Benefit and outcomes
DETAIL [66]	Hypertension+microalbuminuria (5 years)	Telmisartan vs enalapril	Noniferiority renoprotection	Confirmed
CALM [67]	Hypertension+microalbuminuria (24 weeks)	Candesartan+lisnopril vs candesartan vs lisinopril	BP control and microalbunuria reduction	Superiority of combination confirmed
ONTARGET [68]	Hypertension +end organ damage (6 years)	Telmisartan+ramipril vs telmisartan vs ramipril	Proteinuria and renal failure improvement	Combination worsened renal failure
ORIENT [69]	Overt DN (3.2 years)	Olmesaran +ACEI vs ACEI	Proteinuria and renal failure improvement	Cobination did not improved
ADVANCE [70]	Hypertension (4.3 years)	Perindopril+ indapamide vs placebo	Macrro and microvascular events reduction	Confirm combined but not separetly
BENEDICT [71]	Hypertension +normoalbuminuria (3.0 years)	Trandolapril+verapamil vs trandolapril	Albuminuria prevention	Verapamil similar to placebo
AVOID [72]	Hypertension+microalbuminuria (6 months)	Aliskiren+losartan vs.losartan	Albuminuria reduction	Confirmed, independently of BP
Mehdi (2009) [73]	Hypertension+Overt DN (48 weeks)	Spironolactone+lisino. vs losartan+lisino. vs lisinopril	Albuminuria reduction	Combination with spironolactone is superior

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; CV,cardio vascular; DN, diabetic nephropathy;.Lisino, lisinopril. Clinical studies: ABCD, The normotensive Appropriate Blood pressure Control in Diabetes; AVOID, Aliskiren in the Evaluation of Proteinuria in diabetes ; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial CALM, candesartan and lisinopril microalbuminuria; DETAIL, Diabetics Exposed to Telmisartan And enalaprIL; DIRECT, Diabetic Retinopathy Candesartan Trials; IRMA-2, Irbesartan Microalbuminuria in Hypertensive Patients with Type 2 Diabetes; MARVAL,MicroAlbuminuria Reduction With VALsartan ; ONTARGET, Ongoing telmisartan alone and in combination with ramipril global endpoint trial; ORIENT, Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention

Table 1. The benefit of ACEI and ARBS in reducing proteinuria and renal preservation in DN, summary of studies.

11 140 patients with type 2 diabetes were randomised to treatment. After a mean of 4.3 years of follow-up, patients assigned to therapy had a mean reduction in systolic blood pressure of 5.6 mm Hg and diastolic blood pressure of 2.2 mm Hg. The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%]active vs 938 [16.8%]placebo; hazard ratio 0.91, 95% CI 0.83-1.00, p=0.04). The separate reductions in macrovascular and microvascular events were similar but were not independently significant (macrovascular 0.92; 0.81-1.04, p=0.16; microvascular 0.91; 0.80-1.04, p=0.16). The relative risk of death from

cardiovascular disease was reduced by 18% (211 [3.8%] active vs 257 [4.6%] placebo; 0.82, 0.68-0.98, p=0.03) and death from any cause was reduced by 14% (408 [7.3%] active vs 471 [8.5%] placebo; 0.86, 0.75-0.98, p=0.03) [70]. Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) evaluated the effect of calcium channel blockers to prevent albuminuria alone or along with ACEI. studied 1204 subjects, who were randomly assigned to receive at least three years of treatment with trandolapril (at a dose of 2 mg per day) plus verapamil (sustained-release formulation, 180 mg per day), trandolapril alone (2 mg per day), verapamil alone (sustained-release formulation, 240 mg per day), The primary end point was the development of persistent microalbuminuria (overnight albumin excretion,>or =20 ucg per minute at two consecutive visits). The primary outcome was reached in 5.7 percent of the subjects receiving trandolapril plus verapamil, 6.0 percent of the subjects receiving trando-lapril, 11.9 percent of the subjects receiving verapamil, and 10.0 percent of control subjects receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (P=0.01), 0.47 for the comparison between trandolapril and placebo (P=0.01), and 0.83 for the comparison between verapamil and placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Serious adverse events were similar in all treatment groups. The effect of verapamil alone was similar to that of placebo [71]. Aliskiren is an direct renin inhibitor blocks the conversion from angiotensinogen to angiotensin I. In the AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes) study 599 patients with hypertension and type 2 diabetes with nephropathy were randomized to receive aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months) or placebo, in addition to losartan. The primary outcome was a reduction in the ratio of albumin to creatinine. The mean urinary albumin-to-creatinine ratio was reduced by 20% (95% confidence interval, 9 to 30; P<0.001), with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared with 12.5% of those who received placebo (P<0.001). Aliskiren may have renopro-tective effects that are independent of its blood-pressure-lowering effect in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended reno-protective treatment [72]. Aldosterone receptor antagonist, such as spironolactone, has been shown to to reduce proteinuria, when added to ACEI or ARBS. A double-blind, placebo-controlled trial investigated 81 patients with diabetes, hypertension, and albuminuria (urine albumin-to-creatinine ratio > or =300 mg/g) who all received lisinopril (80 mg once daily). The patients were assigned to placebo, losartan (100 mg daily), or spironolactone (25 mg daily) for 48 wk. Compared with placebo, the urine albumin-to-creatinine ratio decreased by 34.0% (95% CI, -51.0%, -11.2%, P = 0.007) in the group assigned to spironolactone and by 16.8% (95% CI, -37.3%, +10.5%, P = 0.20) in the group assigned to losartan [73]. An interesting study assessed the effect of die tary sodium restriction on the efficacy of losartan in hypertensive subjects with type 2 diabetes and albumin excretion rates of 10-200 ucg/min. 20 subjects were randomized to losartan 50 mg/day (n = 10) or placebo (n = 10). Drug therapy was given in two 4-week phases separated by a washout period. In the last 2 weeks of each phase, patients were assigned to low- or regular-sodium diets, in random order. In each phase, 24-h ambulatory blood pressure,

urinary albumin-to-creatinine ratio (ACR), and renal hemodynamics were measured. Achieved urinary sodium on a low-sodium diet was 85 +/- 14 and 80 +/- 22 mmol/day in the losartan and placebo groups, respectively. In the losartan group, the additional blood pressure-lowering effects of a low-sodium diet compared with a regular-sodium diet for 24-h systolic, diastolic, and mean arterial blood pressures were 9.7 mmHg (95% confidence interval [CI], 2.2-17.2; P = 0.002), 5.5 mmHg (2.6-8.4; P = 0.002), and 7.3 mmHg (3.3- 11.3; P = 0.003), respectively. In the losartan group, the ACR decreased significantly on a low-sodium diet versus on a regular-sodium diet (-29% [CI -50.0 to -8.5%] vs. + 14% [-19.4 to 47.9%], respectively; P = 0.02). There was a strong correlation between fall in blood pressure and percent reduction in the ACR (r = 0.7, P = 0.02). In the placebo group, there were no significant changes in blood pressure or ACR between regular- and low-sodium diets [74].

13. Glycemic control

Poor glycemic control is a risk factor for both the development of microalbuminuria and for progression to macroalbuminuria in patients with type 2 diabetes. Strict glycemic control is recommended in all patients because of its beneficial effects on the microvascular complications. Whilst the benefits of intensive glycemic therapy for people with diabetes and microalbuminuria have been well established, controversy remains as to whether intensive therapy slows the progression of established DN, particularly among individuals who have a reduced glomerular filtration rate. In addition, severe hypoglycemia has been associated with intensive glycemic therapy, raising safety concerns that may be of particular relevance for patients with decreased kidney function [75].

14. The ADVANCE study

The ADVANCE study investigated a strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy. 11,140 patients with type 2 diabetes were assigned to undergo either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less. Primary end points were composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), assessed both jointly and separately. Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1%, vs. 20.0% with standard control; hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; P=0.01), as well as that of major microvascular events (9.4% vs. 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01), primarily because of a

reduction in the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P=0.006), with no significant effect on retinopathy (P=0.50) [76].

15. UKPDS

In UKPDS the effects of intensive blood-glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with type 2 diabetes in a randomised controlled trial. 3867 newly diagnosed patients with type 2 diabetes, median age 54 years (IQR 48-60 years), who after 3 months' diet treatment had a mean of two fasting plasma glucose (FPG) concentrations of 6.1-15.0 mmol/L were randomly assigned intensive policy with a sulphonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin, or conventional policy with diet. The aim in the intensive group was FPG less than 6 mmol/L. In the conventional group, the aim was the best achievable FPG with diet alone; drugs were added only if there were hyperglycaemic symptoms or FPG greater than 15 mmol/L. Three aggregate endpoints were used to assess differences between conventional and intensive treatment: any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death); all-cause mortality. Over 10 years, haemoglobin A1c (HbA1c) was 7.0% (6.2-8.2) in the intensive group compared with 7.9% (6.9-8.8) in the conventional group--an 11% reduction. There was no difference in HbA1c among agents in the intensive group. Compared with the conventional group, the risk in the intensive group was 12% lower (95% CI 1-21, p=0.029) for any diabetes-related endpoint; 10% lower (-11 to 27, p=0.34) for any diabetes-related death; and 6% lower (-10 to 20, p=0.44) for all-cause mortality. Most of the risk reduction in the any diabetes-related aggregate endpoint was due to a 25% risk reduction (7-40, p=0.0099) in microvascular endpoints, including the need for retinal photocoagulation [77].

16. Veterans affairs cooperative study

Veterans Affairs Cooperative Study proved that intensive glycemic control retards microalbuminuria in patients who have had type 2 diabetes for several years but may not lessen the progressive deterioration of glomerular function. 153 male patients to either intensive treatment (INT) (goal HbA(1c) 7.1%) or to standard treatment (ST) (goal HbA(1c) 9.1%; P = 0.001), and data were obtained during a 2-year period. Mean duration of known diabetes was 8 years, mean age of the patients was 60 years, All patients were treated with insulin. INT retarded the progression of microalbuminuria during the 2-year period: the changes in albumin:creatinine ratio from baseline to 2 years of INT versus ST were 0.045 vs. 0.141, respectively (P = 0.046). Retardation of progressive urinary albumin excretion was most

pronounced in those patients who entered the study with microalbuminuria and were randomized to INT. Patients entering with microalbuminuria had a deterioration in creatinine clearance at 2 years regardless of the intensity of glycemic control. The unexplainined finding was that in the group entering without microalbuminuria, the subgroup receiving ST had a lower percentage of patients with a macrovascular event (17%) than the subgroup receiving INT (36%) (P = 0.03) [78].

17. ACCORD

ACCORD study concluded that microvascular benefits of intensive therapy should be weighed against the increase in total and cardiovascular disease-related mortality, increased weight gain, and high risk for severe hypoglycaemia. 10251 patients were randomly assigned, 5128 to the intensive glycaemia control group and 5123 to standard group. Intensive therapy was stopped before study end because of higher mortality in that group, and patients were transitioned to standard therapy. At transition, the first composite outcome was recorded in 443 of 5107 patients in the intensive group versus 444 of 5108 in the standard group (HR 1.00, 95% CI 0.88-1.14; p=1.00), and the second composite outcome was noted in 1591 of 5107 versus 1659 of 5108 (0.96, 0.89-1.02; p=0.19). Results were similar at study end (first composite outcome 556 of 5119 vs 586 of 5115 [HR 0.95, 95% CI 0.85-1.07, p=0.42]; and second 1956 of 5119 vs 2046 of 5115, respectively [0.95, 0.89-1.01, p=0.12]). Intensive therapy did not reduce the risk of advanced measures of microvascular outcomes, but delayed the onset of albuminuria and some measures of eye complications and neuropathy [79].

18. VADT

VADT study investigated the intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications with the exception of progression of albuminuria (P = 0.01). 1791 military veterans (mean age, 60.4 years) who had a suboptimal response to therapy for type 2 diabetes were assigned to receive either intensive or standard glucose control. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated hemoglobin level, as compared with the standard-therapy group. The primary outcome was the time from randomization to the first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. The median follow-up was 5.6 years. Median glycated hemoglobin levels were 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. The primary outcome occurred in 264 patients in the standard-therapy group and 235 patients in the intensive-therapy group (hazard ratio in the intensive-therapy group, 0.88; 95% confidence interval [CI], 0.74 to 1.05; P=0.14). There was no significant difference between the two groups in any component of the primary outcome or in the rate of death from any cause (hazard ratio, 1.07;

95% CI, 0.81 to 1.42; P=0.62). No differences between the two groups were observed for microvascular complications. The rates of adverse events, predominantly hypoglycemia, were 17.6% in the standard-therapy group and 24.1% in the intensive-therapy group [80].

19. Kumato study

Kumato study investigated a total of 110 Japanese patients with type 2 diabetes (55 with no retinopathy [the primary prevention cohort] and 55 with simple retinopathy [the secondary intervention cohort]) in an 8-year prospective study. The patients were randomly assigned to multiple insulin injection therapy (MIT) groups and administered three or more daily insulin injections or assigned to conventional insulin injection therapy (CIT) groups and administered one or two daily intermediate-acting insulin injections. Worsening of microvascular complications was regularly assessed during 8 years. In both primary prevention and secondary intervention cohorts, the cumulative percentages of worsening in retinopathy and nephropathy were significantly lower (P < 0.05) in the MIT group than in the CIT group. In neurological tests after 8 years, the MIT group showed significant improvement (P < 0.05) in the median nerve conduction velocities (motor and sensory nerves), whereas the CIT group showed significant deterioration (P < 0.05) in the nerve conduction velocities and vibration threshold. From this study, the glycemic threshold to prevent the onset and progression of diabetic microvascular complications was as follows: HbA1c < 6.5%, fasting blood glucose concentration < 110 mg/dl, and 2-h postprandial blood glucose concentration < 180 mg/dl [81]. Moreover, antihypertensive therapy and improved glycaemic control were independent predictors for remission. 151 patients with type 2 diabetes and microalbuminuria at baseline in whom GFR was measured at least three times during 7.8 years of follow-up were divided into three groups according to the level of albuminuria during follow-up. Overt nephropathy was diagnosed as a UAER>300 mg/24 h and remission to normoalbuminuria was defined as an UAER<30 mg/24 h at the last examination. During follow-up, 46 patients achieved remission to normoalbuminuria, 58 remained microalbuminuric and 47 patients progressed to overt nephropathy. The mean (+/- SE) yearly decline in GFR was lowest (2.3+/-0.4 ml/min/year) in patients who obtained remission, in comparison with patients remaining microalbuminuric, in whom the decline was 3.7+/-0.4 ml/min/year, and patients progressing to overt nephropathy, who had a decline in GFR of 5.4+/-0.5 ml/min/year (ANOVA, P<0.001). Start of antihypertensive treatment during follow-up was strongly associated with remission to normoalbuminuria [odds ratio: 2.32; 95% confidence interval (CI): 1.09-4.93] whereas a decrease in HbA(1c) by 1% increased the probability for remission (odds ratio: 1.48; 95% CI: 1.11-1.97) [82]

20. Other diabetic treatment strategies

Other treatments were developed in addition to blood pressure control, glucose control and renin-angiotensin system blockade to slow kidney function deterioration. We will briefly discuss some of them.

- Vitamin D receptor (VDR) agonists. The main sources of vitamin D3 are diet and skin under the influence of solar ultraviolet action. Vitamin D3 is activated to 1,25dihydroxyvitamin D3 [1,25(0H)2 D3] by liver and kidney. VDR agonists are renal protective in diabetic patients. VDR agonists slow renal fibrosis through RAS blockade and have synergic effects in combinations ACE inhibitors or ARBS [83]. Two of VDR agonists, doxercalciferol and paricalcitol decrease proteinuria. Doxercalciferol effect was investigated in diet-induced obesity mice Proteinuria,, renal mesangial expansion and podocytes injury were slowed by doxercalciferol. Doxercalciferol also diminished oxidative stress, macrophage infiltration and profibrotic growth factors [84]. Paricalcitol was investigated in Vital study. Paricalcitol had a synergic effect with ACE inhibitors and ARBs and reduced proteinuria in type 2 diabetic patients [85].

- Farnesoid X receptor agonists (FXR). The hydrophobic bile acid, chenodeoxycholic acid, activates FXR and has an important role in preventing atherosclerosis, and controlling metabolic and bile acid homeostasis [86]. FXR was detected in kidney and other organs like liver and adrenal gland [87]. FXR agonists was investigated in FXR knockout mice. The studies proved that FXR agonists diminished proteinuria, glomerulosclerosis, tubulointerstital fibrosis and macrophage infiltration [85,88].

- AGEs inhibitors. The clinical utility of these agents remain to be proven. Studies with aminoguanidine (pimagenide) were interrupted due to safety concern. AGE breakers (N-phenacylthiazodium bromide and alagebrium chloride), anti-RAGE antibodies were used only in experimental models. Pyridoxamine (vitamin B6 derivate), an AGEs inhibitor, reduced proteinuria in several studies [89,90].

Pirfenidone and Bartoxolone. Pirfenidone [5-methyl-1-phenyl-2(1H)-pyrodone] is a synthetic antifibrotic agent. Pirfenidone blocks TGF- β promoter and secretron and reduces tubular and glomerural lesions in experimental models [91]. Bardoxolone has an antiinflamatory effect and acts through Nrf2 pathway. Nrf2 is a transcription factor controlling antioxidant genes that help maintain redox homeostasis. A phase 2, double-blind, randomized, placebo-controlled trial investigated the role of bardoxolone. 227 adults with CKD (defined as an estimated glomerular filtration rate [GFR] of 20 to 45 ml per minute per 1.73 m(2) of body-surface area) in a 1:1:1:1 ratio were assigned to receive placebo or bardoxolone methyl at a target dose of 25, 75, or 150 mg once daily. The primary outcome was the change from baseline in the estimated GFR with bardoxolone methyl, as compared with placebo, at 24 weeks; a secondary outcome was the change at 52 weeks. Patients receiving bardoxolone methyl had significant increases in the estimated GFR, as compared with placebo, at 24 weeks (with between-group differences per minute per 1.73 m(2) of 8.2±1.5 ml in the 25-mg group, 11.4±1.5 ml in the 75-mg group, and 10.4±1.5 ml in the 150-mg group; P<0.001). The increases were maintained through week 52, with significant differences per minute per 1.73 m^2 of 5.8±1.8 ml, 10.5±1.8 ml, and 9.3±1.9 ml, respectively. Muscle spasms, the most frequent adverse event in the bardoxolone methyl groups, were generally mild and dose-related. Hypomagnesemia, mild increases in alanine aminotransferase levels, and gastrointestinal effects were more common among patients receiving bardoxolone methyl [92].

21. Conclusion

Microalbuminuria and proteinuria are common complications among patients with type 2 diabetes. Proteinuria is a predictive factor for cardiovascular events, and cardiovascular and all-cause mortality. Microalbuminuria is defined as persistent urinary albumin excretion between 30 and 300 mg/day (20 to 200 µg/min). Macroalbuminuria refers to albumin excretion above 300 mg/day (200 µg/min). Patients with diabetes mellitus type 2 must be screened annually for proteinuria, starting at diagnosis. Measurement of the albumin:creatinine ratio in a first-morning void is the superior method to predict renal events in patients with type 2 diabetes and nephropathy, but the difference compared to spot urine samples at other times was not significant. Intervention studies in microalbuminuric type 2 diabetic patients have demonstrated that it is possible to avoid progression to overt diabetic nephropathy and even to achieve regression to normoalbuminuria. The best therapeutic strategy is a multifactorial approach including glycemic control, blood pressure control, renin-angiotensin inhibition and lifestyle modification.

Author details

Relu Cernes[1] and Reuven Zimlichman[2]

1 Department of Nephrology and The Brunner Institute for Cardiovascular Research, Wolfson Medical Center and Tel Aviv University, Israel

2 Chief Department of Medicine and The Brunner Institute for Cardiovascular Research, Wolfson Medical Center and Tel Aviv University, Israel

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