Kidney disease in diabetology: lessons from 2009

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Introduction

Diabetic nephropathy (DN) is the worldwide most common cause of renal failure requiring renal replacement therapy, but today most patients have type 2 and not type 1 diabetes. During the last 30 years the rate of type 1 diabetic patients requiring renal replacement therapy decreased continuously due to significant improvement of antидiabetic and antihypertensive treatment strategies. The landmark study DCCT (Diabetes Control and Complications Trial) showed that a mean reduction in HbA1C by 2% reduced the incidence of nephropathy by 54% and retinopathy by 76% [1]. A recent report [2] from the DCCCT indicates that after 30 years of diabetes, the cumulative incidences of proliferative retinopathy, DN, and cardiovascular disease (CVD) were as high as 50%, 25% and 14% in the conventional treatment group (mean HbA1c: 9%), but only 21%, 9% and 9% in the intensive treatment group (mean HbA1c: 7%). Interestingly, less than 1% in the intensive treated patient group became blind, required kidney replacement or needed an amputation because of diabetes during that time. The increased burden arriving from type 2 diabetes is explained not only by the worldwide pandemia of that disease, but also by the much longer life expectancy. Before 1980 most patients with type 2 diabetes died before they progressed to end stage renal disease (ESRD). Recently, good news were reported from the Framingham study [3] indicating that type 2 diabetic patients had a 69% decline in CVD mortality similar to patients without diabetes (62% decline) during the last 25 years (1976–2005) compared with the earlier period between 1950 and 1975. Compared with individuals without diabetes mellitus, individuals with diabetes experienced a greater increase in body mass index, a greater decrease in low-density lipoprotein cholesterol and a similar magnitude of decline in systolic blood pressure [4]. However, diabetic individuals have not experienced the necessary declines in CVD risk factors to overcome this increased CVD risk and to protect them from progressing to ESRD after long duration of diabetes.

Chronic kidney disease is a dominant predictor for excess mortality in type 1 diabetes

Despite modern therapeutics, type 1 diabetes continues to be associated with premature death. Mortality in individuals with type 1 diabetes is about 3–4 times higher than in the...
general population. Recent findings [5] from the Finnish Diabetic Nephropathy (FinnDiane) study clearly demonstrate that chronic kidney disease (CKD) is the dominant contributor to this excess mortality. During a median 7 years of follow-up of 4201 adults—presenting with relative high mean HbA1c levels of 8.6%—there were 291 deaths (7%), 3.6-fold more than that observed in the age- and sex-matched general population. Remarkably, excess mortality was only observed in patients with CKD, whereas individuals with normoalbuminuria showed no excess mortality (SMR: standardized mortality ratio 0.8) independent of the duration of diabetes. The presence of microalbuminuria, macroalbuminuria and end-stage renal disease (ESRD) was associated with 2.8, 9.2 and 18.3 times higher SMR ratios compared with nondiabetic individuals. The FinnDiane study also demonstrated that estimated glomerular filtration rate (eGFR) is an independent risk factor for mortality in type 1 diabetes. Regardless of the level of albuminuria, those with an eGFR <60 ml/min per 1.73 m² were twice as likely to have died during follow-up. In addition, individuals with an eGFR >120 ml/min per 1.73 m² also displayed increased mortality compared with those with normal renal function (unadjusted mortality 3 versus 1%, \( P = 0.01 \)).

**HbA1C variability is predictive of incident microalbuminuria, progression of renal disease and incident CVD events in type 1 diabetes**

It has been debated whether glycaemic variability confers additional risk of diabetes complications in addition to the level of long-term glycaemia. Patients with identical HbA1C values may still show large variation in their glycaemic excursions. In theory, a highly variable glucose profile could confer a greater risk of diabetes complications through increased oxidative stress [6]. In fact, a recent analysis of the DCCT data indicated that variation in the long-term glycaemia, defined as intrapersonal standard deviations (SDs) of quarterly measured HbA1C, added to the predictive value of HbA1C level alone for both nephropathy and retinopathy [7]. This is a potentially important clinical finding, but since the DCCT was an intervention study focusing on HbA1C, the results might not reflect the situation in a normal clinical setting. Therefore, the effect of both the mean HbA1C and the variability of HbA1C on the prediction of diabetes complications was analyzed in the observational, longitudinal Finnish Diabetic Nephropathy (FinnDiane) Study [8]. A total of 2107 patients had complete data on renal status and serial measurements of HbA1C from baseline to a median follow-up of 5.7 years. Intrapersonal SDs of serially measured HbA1C were considered a measure of variability. Intrapersonal mean of serially measured HbA1C was 8.5% and SD 0.78. There was a clear correlation between baseline single-measured HbA1c and the mean of serial HbA1c (\( r = 0.72, P = 0.001 \)). During follow-up, 10.2% progressed to a higher albuminuria level or to ESRD, whereas 8.6% had a CVD event. The SD of serial HbA1C was 1.01 versus 0.75 (\( P = 0.001 \)) for renal status and 0.87 versus 0.79 (\( P = 0.023 \)) for CVD in progressors versus nonprogressors, respectively. In a Cox regression model, SD of serial HbA1C was independently associated with progression of renal disease (HR 1.92) and of a CVD event (1.98) even when adjusting for mean HbA1C and traditional risk factors. Interestingly, mean serial HbA1C itself was not predictive for CVD even though the SD of HbA1C was. In conclusion, in patients with type 1 diabetes, HbA1C variability was not only predictive of incident microalbuminuria and progression of renal disease but also of incident CVD events.

**High serum uric acid and lipid abnormalities are predictors for development of or progression of diabetic nephropathy in type 1 diabetes**

Experimental and clinical studies have suggested that uric acid may contribute to the development of hypertension and kidney disease. In a prospective observational follow-up study, 277 patients were followed from onset of type 1 diabetes [9]. During a median follow-up of 18.1 years, 23 of 263 patients developed persistent macroalbuminuria (urinary albumin excretion rate >300 mg/24 h). In patients with uric acid levels in the highest quartile (>249 mol/l), the cumulative incidence of persistent macroalbuminuria was 22.3% compared with 9.5% in patients with uric acid in the three lower quartiles (\( P = 0.006 \)). In conclusion, a high uric acid level soon after onset of type 1 diabetes is independently associated with an increased risk for later development of diabetic nephropathy.

Already 30 years ago [10], it was shown that both type 1 and type 2 diabetic patients show many lipid abnormalities including HDL-cholesterol, triglycerides, VLDL and apolipoproteins A-I, A-II and B when compared with carefully selected controls matched for sex, age and body weight. Since glycaemic control cannot normalize all lipid abnormalities in diabetic patients [11] lipid-lowering drugs are now widely recommended for these patients. Multiple lipid abnormalities are already present at an early stage of diabetic nephropathy in patients with type 1 diabetes and earlier small studies have suggested that lipid variables might be involved in the development and progression of diabetic nephropathy, but it can also be argued that the lipid abnormalities are merely a consequence of albuminuria. Therefore, the impact of baseline lipid variables on the progression of renal disease was studied in the large Finnish prospective study of patients with type 1 diabetes (FinnDiane), whereby 2304 patients were followed for 5.4 years [12]. High triacylglycerol, apolipoprotein (Apo) B, ApoA-II and HDL3-cholesterol concentrations predicted incident microalbuminuria. Progression to macroalbuminuria was predicted by high triacylglycerol and ApoB. When albumin excretion rate (AER) was entered into the model, triacylglycerol was no longer an independent predictor, but when patients with normal AER and microalbuminuria at baseline were pooled, triacylglycerol, HbA1c, male sex and AER were all independent predictors of renal disease. High total cholesterol, LDL-cholesterol, non-HDL-cholesterol and triacylglycerol as well as low HDL-cholesterol, HDL2-cholesterol, ApoA-I and ApoA-II concentrations were predictive of progression to end-stage renal disease.
renal disease. However, when estimated GFR was entered into the model, only total cholesterol remained an independent predictor of progression. In conclusion, lipid abnormalities, particularly high triacylglycerol concentrations, increase the risk of progression of renal disease. Whether lower lipid targets than those currently recommended would be beneficial with regard to progression of renal disease remains an open question.

Improved outcome in type 1 diabetic pregnant women with microalbuminuria or diabetic nephropathy

Type 1 diabetic women with microalbuminuria or diabetic nephropathy are at particular risk of poor pregnancy outcome [13]. Diabetic nephropathy is associated with a high risk of gestational hypertension, preeclampsia and preterm delivery [14]. Likewise, preeclampsia and preterm delivery occur more frequently in type 1 diabetic women with microalbuminuria. ACE inhibitors are effective drugs reducing the risk of renal complications in both type 1 diabetic patients with microalbuminuria and diabetic nephropathy. Unfortunately ACE inhibitors cannot be used during pregnancy, since ACE inhibition in early pregnancy has been associated with congenital malformations [15], while use late in pregnancy may cause foetal renal failure [16]. ACE inhibition therefore should be discontinued before conception or as soon as pregnancy is confirmed.

In a Danish prospective study [17] of 117 pregnant women with type 1 diabetes (100 with normoalbuminuria, 10 with microalbuminuria and 7 with diabetic nephropathy) antihypertensive therapy, mainly methyldopa, was given to obtain blood pressure <135/85 mmHg and urinary albumin excretion <300 mg/24 h. The pregnancy outcome was compared with recently published studies of pregnant women with microalbuminuria or diabetic nephropathy. Mean systolic blood pressure during pregnancy was 120 mmHg (range 101–147), 122 mmHg (116–135) and 135 mmHg (111–145) in women with normoalbuminuria, microalbuminuria and diabetic nephropathy, respectively ($P = 0.009$). The frequency of preterm delivery was 20% in women with normoalbuminuria and microalbuminuria, in contrast to 71% in women with diabetic nephropathy ($P = 0.01$) where the median gestational age was 258 days (220–260). Compared with previous studies using less stringent antihypertensive therapeutic strategy and less strict metabolic control, gestational age was longer and birth weight was larger in this study. Birth weight did not differ between infants of women with normoalbuminuria and microalbuminuria but was lower in women with diabetic nephropathy ($P = 0.017$). Furthermore infants of women with diabetic nephropathy more often were small-for-gestational-age ($P = 0.01$). None of the women with microalbuminuria developed preeclampsia, but three of the seven women with diabetic nephropathy had preeclampsia, indicating that the risk is still increased in these patients with long duration of diabetes and advanced microvascular disease. In conclusion, with intensified antihypertensive therapy and strict metabolic control, comparable pregnancy outcome was seen in type 1 diabetic women with microalbuminuria and normoalbuminuria. Although less severe than in previous studies, diabetic nephropathy was associated with more adverse pregnancy outcome.

Early RAS blockade does not slow nephropathy progression in patients with type 1 diabetes

Nephropathy and retinopathy remain important complications of type 1 diabetes. Since it was unclear whether their progression is slowed by early administration of drugs that block the renin–angiotensin system (RAS), a controlled trial in 285 normotensive patients with type 1 diabetes and normoalbuminuria was initiated [18]. The patients were randomly assigned to receive losartan (100 mg daily), enalapril (20 mg daily), or placebo and were followed for 5 years. The study by Mauer et al. [18] is extraordinary, since it compares two strategies for inhibition of the RAS, it is the longest study in this field and evaluated three important renal key parameters, the presence or absence of microalbuminuria and of renal morphologic features, the GFR, as well as the progression of retinopathy. Surprisingly, inhibition of the RAS system did not reduce the incidence of microalbuminuria and mitigated neither the decline of renal function nor the development of morphologic lesions. The 5-year cumulative incidence of microalbuminuria was 6% in the placebo group and was significantly higher in the losartan group (17%; $P = 0.02$) but not with enalapril (4%, $P = 0.96$). In contrast to its failure to prevent development of early nephropathy, however, inhibition of the RAS reduced the advancement of retinal changes by 60 to 70% as compared with placebo, most likely independently of blood-pressure reduction. Based on these findings it seems that the pathologic mechanisms of early complications of diabetes are heterogeneous. Inhibition of the RAS can prevent early retinopathy, but not early nephropathy. This is in sharp contrast to the situation in more advanced stages of diabetic complications, in which inhibition of the RAS system mitigates the loss of renal function without apparent influence on retinopathy progression [19].

Disappointing results with the treatment of renal anaemia in type 2 diabetes

Increasing evidence indicates that anaemia in patients with renal impairment contributes to considerable morbidity and mortality of CVD and may speed progression to end-stage renal failure in diabetic patients. Since effective treatment for anaemia associated with renal impairment is available since 20 years and is now widely used, prospective trials of early erythropoietin intervention in patients with diabetic kidney disease (DKD) were urgently required to clarify whether this intervention is of benefit or causes harm. It was hoped that early correction of anaemia in patients with DKD may slow progression of renal impairment and could reduce CVD morbidity and improve patient survival in these patients. Recently, very disappointing primary end-point results were published [20] of the Trial
to Reduce Cardiovascular Events with Aranesp Therapy (TREAT). This large, randomized, double-blind, placebo-controlled clinical trial was designed to determine whether the treatment of anaemia with an erythropoiesis-stimulating agent (ESA), namely, darbepoetin alfa, would reduce the risk of death, major CVD events and renal events among type 2 diabetic patients with CKD and anaemia. In total 4038 type 2 diabetic patients with CKD (mean eGFR 34 ml/min, mean serum creatinine 1.8 mg/dl) and moderate iron-replete anaemia were included; median age was 68 years, two-thirds had a history of CVD and the median follow-up period was 29.1 months. Overall the patients were relatively well treated for diabetes and CVD risk factors resulting in acceptable control parameters: HbA1c 6.9%, LDL-cholesterol 80 mg/dl, blood pressure 135/70 mm Hg. The risk of death and major CVD event was 31% in the entire cohort over the course of the trial, a reminder of the incredible burden of CVD in type 2 diabetic patients with chronic kidney disease.

The median achieved haemoglobin concentrations were 12.5 g/dl in the patients who received an ESA and 10.6 g/dl in the patients who received placebo. Death or a CVD event occurred in 632 patients assigned to darbepoetin alfa and 602 patients assigned to placebo (HR 1.05; \( P = 0.41 \)). Likewise, death or ESRD occurred in 652 patients assigned to darbepoetin alfa and 618 patients assigned to placebo (HR 1.06; \( P = 0.29 \)). Remarkably, fatal or nonfatal stroke occurred in 101 patients assigned to darbepoetin alfa and 53 patients assigned to placebo (HR 1.92; \( P < 0.001 \)). Among the 348 patients with a history of cancer at baseline, mortality was significantly higher (\( P = 0.002 \)) in the patients receiving darbepoetin alfa (14 of 188 patients died from cancer) than under placebo (only 1 of the 160 patients died): These findings are consistent with those in the TREAT study, Pfeffer et al. [21]. Based on the findings of the TREAT study, Pfeffer et al. [20] concluded that, in many patients with diabetes, chronic kidney disease and moderate anaemia who are not undergoing dialysis, the increased risk of stroke and possibly death among patients with a history of a malignant condition will outweigh any potential benefit of an ESA.

Conflict of interest statement. None declared.

References


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