Kidney Disease in Diabetology: Lessons from 2008

Guntram Schernthaner

Department of Medicine I, Rudolfstiftung Hospital, Vienna, Austria

Keywords: ADVANCE; AVOID; DIRECT; microalbuminuria; ONTARGET

Introduction

Micro- and macroalbuminuria are important markers for early and progressive diabetic kidney disease. Patients with type 1 diabetes carry a 20–50% risk of developing end-stage renal disease (ESRD) requiring dialysis or renal transplantation. The primary goal of managing childhood type 1 diabetes is to prevent or delay renal and retinal microvascular complications. In contrast to patients with type 2 diabetes, the cumulative incidence of nephropathy has significantly declined in patients with type 1 diabetes over the past three decades, which was due to more intensified treatment regimens for control of hyperglycaemia, hypertension and dyslipidaemia. However, many patients with type 1 diabetes have their manifestation of disease already at very young age, when strict diabetes control is more difficult to reach compared to patients with manifestation of diabetes later in life.

Microalbuminuria in Type 1 Diabetic Children

Most of our knowledge of the relationship between control of diabetes and the risk of diabetic renal complications comes from data in adults and adolescents, so it is important to have a precise evaluation of the risk in children. Two recent studies performed in diabetic children in Germany [1] and in the UK [2] indicate that insufficient glycaemic control in diabetic childhood is an important contributor to the overall risk of developing diabetic kidney disease. In a nationwide, prospective German Diabetes Study [1] 27 805 patients who had at least two documented urine analyses with identical classification were included. The median age at diagnosis of type 1 diabetes was 9.9 years (interquartile range 5.8–14.3), and age at last visit was 16.3 years (12.5–22.2), with a mean HbA1c of 8.0%. Nephropathy was classified as normal in 26 605, microalbuminuric in 919, macroalbuminuric in 78 and end-stage renal disease (ESRD) in 203 patients. After calculated diabetes duration of 40 years, 25.4% had microalbuminuria and 9.4% had macroalbuminuria or ESRD. Significant risk factors for microalbuminuria were diabetes duration, HbA1c, LDL cholesterol and blood pressure, while diabetes onset at childhood was protective. Male sex was associated with the development of microalbuminuria.

The UK study [2] is a prospective observational study performed in 527 diabetic children with a diagnosis of type 1 diabetes at the mean age of 8.8 years and the mean follow-up of 9.8 years. Mean HbA1c at diagnosis of diabetes was 10.9% and 9.7% at end of the observation (P < 0.001). The cumulative prevalence of microalbuminuria was 25.7% after 10 years of diabetes and 50.7% after 19 years of diabetes and 5182 patient-years of the follow-up. The main result of the study is that mean HbA1c is a strong predictor—and the only modifiable one identified—of microalbuminuria, with a hazard ratio of 1.39, for each 1% increase of HbA1c. The study did not directly assess whether an HbA1c threshold existed below which the risk of microalbuminuria is null or minimal. However, the group with a mean HbA1c lower than 8.5%, the best-controlled group of children in the study, was not protected—these patients had around a 15% risk of microalbuminuria at the age of 20 years. In this study, only 15% of patients with microalbuminuria were treated by ACE inhibitors (ACE-I), limiting adequate assessment of the potential role of blood pressure (BP) modification.

The role of the control of diabetes during childhood—as opposed to later in life—in determining the risk of complications is important because the complications of diabetes are first identified after the onset of puberty, even in patients with early onset of disease. Both studies performed in diabetic children in Germany and in Oxford clearly demonstrate that the risk for developing diabetic kidney disease is much higher as previously believed. Since the long-term risk after 40 years was also about 10% for macroalbuminuria or ESRD in the diabetic children despite a much lower HbA1c level of about 8%, the future potential for further decreasing the risk in diabetic children seems to be limited. This suspicion is supported by a recent analysis of glycaemic control in 1041 type 1 diabetic children and adolescents treated by insulin pumps in 30 leading Centres for
Care Treatment of Diabetic Children in 16 European countries and Israel [3]. Although the diabetes control level was significantly improved during the last 10 years in diabetic children, the mean HbA1c in that study was still 8.0 ± 1.3%.

A small proportion (15%) of diabetic children with microalbuminuria in the UK study [2] were treated with antihypertensive drugs (ACE-I) with rather unsatisfactory results, limiting adequate assessment of the potential role of BP modification. Since no data are available on the use of ACE-I or angiotensin II receptor blockers (ARBs) in adolescents with diabetic nephropathy, intervention trials are needed to evaluate whether treatments recommended for adults with microalbuminuria are similarly reno-protective in adolescents.

**Prevention of microalbuminuria in diabetic patients by ARB treatment: lessons from DIRECT**

Specific drugs to lower BP, particularly inhibitors of the renin–angiotensin system (RAS), have been hypothesized to have additional beneficial effects on diabetic microvascular disease, independent of their absolute hypotensive actions. In the DIRECT (diabetic retinopathy Candesartan trials) study [4,5], 5231 patients with type 1 or type 2 diabetes were randomized to placebo or 32 mg candesartan, an ARB, daily. All patients, normoalbuminuric, and either normotensive or only mildly hypertensive at entry of the study, were followed for 4 years. The findings of the primary endpoints—prevention and progression of diabetic retinopathy in type 1 diabetes [4] and progression and regression of diabetic retinopathy in type 2 diabetes [5]—were recently published. The effects of candesartan on the development of microalbuminuria have not yet been published, but were recently reported by Bilous at the EASD Congress in Rome. In the combined cohort of type 1 and type 2 diabetic patients, mean age was 40 years and mean diabetes duration was 9 years. Mean HbA1c was relatively high at the study entry with 8.3%, but remained unchanged during the 4 years of follow-up. The majority of patients (77%) were normotensive (blood pressure 118/74 mmHg) and blood pressure was also relatively well treated in the 23% of patients presenting with hypertension (blood pressure 139/79 mmHg). Despite the fact that candesartan reduced the mean BP by 3.6/2.7 mmHg in comparison with placebo, the DIRECT-renal analysis did not demonstrate a significant effect of RAS blockade on the primary prevention of microalbuminuria. The risk of developing microalbuminuria in normoalbuminuric patients was reduced by only 5% over a 4.4-year period on candesartan [hazard ratio 0.95, 95% CI 0.78, 1.16 (P = 0.1)]. Interestingly, the incidence of microalbuminuria was much lower (about only 9% over 5 years) than expected from previous studies performed at the end of the last century.

**Risk for diabetic nephropathy in type 2 diabetes can be reduced by 33% when both hyperglycaemia and BP are better controlled: results from ADVANCE**

In the ADVANCE (action in diabetes and vascular disease: preterAx and diamicroN-MR controlled evaluation) trial, the effects of routine BP lowering (regardless of BP level) and intensive lowering of blood glucose levels were evaluated in 11140 patients with type 2 diabetes and with a high risk of cardiovascular (CV) events [4,5]. At start of the trial, mean duration of diabetes was 8 years, mean BP was 145/81 mmHg and mean HbA1c was 7.2%. After a mean follow-up for 4.3 years, systolic and diastolic BP were reduced in the active treatment (perindopril and indapamide) by 5.6 mmHg and 2.2 mmHg, respectively, versus standard PB treatment [4]. The relative risk of major macro- and microvascular events was reduced by 9% (P = 0.04), and all-cause mortality by 14% (P = 0.025). Active BP treatment was associated with a significant 21% reduction [4] in all renal events (P < 0.0001), with a borderline significant reduction in new or worsening nephropathy (3.3% versus 3.9%; relative risk reduction 18% (P = 0.055) and a significant reduction in the development of microalbuminuria (19.6% versus 23.6%; 21% (P < 0.0001). Over 5 years, one patient in every 20-assigned active treatment would have avoided one renal event, mostly the onset of new microalbuminuria [4]. Intensive glucose control in the ADVANCE trial [5] resulted in a significant reduction in renal events, including new or worsening nephropathy (HR 0.79; P = 0.006) and new-onset microalbuminuria (HR 0.91; P = 0.02), compared with the glucose control arm (HbA1c levels at study end were 6.4% versus 7.0%). The greatest benefit associated with intensive glucose control was seen for the development of macroalbuminuria (2.9%, versus 4.1% with standard control; HR 0.70; P < 0.001), with a trend towards a reduction in the need for renal replacement therapy or death from renal causes (0.4% versus 0.6%; hazard ratio, 0.64; P = 0.09) but no effect on the doubling of serum creatinine level (1.2% versus 1.1%). The most impressive effect was seen when the joint effect of BP lowering and intensive glucose control was analysed in ADVANCE (Chalmers et al. EASD Congress Rome 2008); new or worsening nephropathy was reduced by RRR of 33% (P = 0.005) in the patients with type 2 diabetes.

**Progression from microalbuminuria to macroalbuminuria despite blockade of RAS with ACE-I**

Recent studies demonstrated that microalbuminuria returns to normoalbuminuria in at least half of patients with type 1 diabetes [6,7]. During the past decade, several clinical trials demonstrated the effectiveness of ACE-I in retarding the progression of microalbuminuria to proteinuria and in slowing the rate of renal function decline in patients with proteinuria [8–11]. However, the progression of microalbuminuria occurs frequently despite ACE-I treatment, and its major determinants/predictors are poor glycaemic control and elevated serum cholesterol [7,9]. In the 7-year follow-up study of 352 microalbuminuric type 1 diabetic patients from 31 European centres in the EURODIAB trial, 13.9% of the microalbuminuric patients progressed to macroalbuminuria, 35.5% remained microalbuminuric and 50.6% reverted to normoalbuminuria [7]. Independent baseline risk factors for progression to macroalbuminuria were HbA1c (7.9% versus 6.8%, P = 0.004), albumin excretion rate (AER) (64.4 versus 44.9 µg/min, P = 0.0001). BP levels at
baseline were not higher in those patients who progressed to macroalbuminuria compared to those who did not progress (127 ± 19.0 mmHg versus 125 ± 17.8, P = NS), whereas HbA1c values were significantly higher already at baseline in the progressors (7.9 ± 2.0 versus 6.8 ± 1.8; P = 0.004). After 7 years of follow-up, systolic BP was significantly higher in those who progressed to macroalbuminuria (136 ± 22 mmHg) than in those who remained microalbuminuric (125 ± 21 mmHg) or reverted to normoalbuminuria (120 ± 18 mmHg) (P < 0.01). As expected, significantly (P < 0.001) more patients were on BP lowering agents in those who progressed to macroalbuminuria (57%) compared to nonprogressors (42%) or to those who reverted to normoalbuminuria (24%).

Progression occurred despite the fact that 88% of those patients received ACE-I. Interestingly, moderate alcohol consumption (30–210 g/week) decreased significantly (P = 0.008) the risk for macroalbuminuria (odds ratio 0.36–0.46) compared with those patients who had no or very low alcohol intake [8]. A recent 10-year observational study of 373 type 1 diabetic patients from the Harvard University Clinic confirms that a considerable number of patients with microalbuminuria progress to macroalbuminuria despite ACE-I treatment [12]. That study additionally provides strong support for the role of chronic hyperglycaemia as a major determinant/predictor of glomerular damage even in the presence of treatment with ACE-I. Progression from microalbuminuria to proteinuria despite ACE-I therapy may result from incomplete patient adherence to therapy or from insufficient biological efficacy of these medications.

**Is double blockade of RAS by ARB plus renin inhibition superior to ACE plus ARB? Lessons from ONTARGET and AVOID**

In 2000, the CALM study evaluating the dual blockade of the RAAS by candesartan and lisinopril in patients with hypertension, microalbuminuria and type 2 diabetes showed rather promising results [13]. However, the effectiveness of the dual RAAS blockade in reducing systolic and diastolic BP by 10 mmHg and 6 mmHg in reducing albuminuria could not be confirmed in larger and longer studies [14,15]. In the IMPROVE study, the dual RAAS blockade with ramipril and irbesartan in 405 hypertensive diabetic patients did not reduce microalbuminuria to a greater extent than treatment with ramipril alone [14]. In the ONTARGET (ONGOing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study, dual blockade of RAAS was evaluated in 25,620 patients with vascular disease or high-risk diabetes (n = 6982), who were followed for 5 years [15]. 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 (13.4%) and ramipril (13.5%), but was increased with the combination therapy (14.5%; HR 1.09; P = 0.037). The secondary renal outcome, dialysis or doubling of serum creatinine, was similar with telmisartan [2.21% and ramipril 2.03% but more frequent with the combination therapy (2.49%; HR 1.24; P = 0.038)]. The estimated glomerular filtration rate (eGFR) declined less with ramipril, compared with telmisartan (−2.82 mL/min/1.73 m² versus −4.12, P < 0.0001) or combination therapy (−6.11; P < 0.0001). By contrast, the increase in urinary albumin excretion was less with telmisartan (P = 0.004) or with combination therapy (P = 0.001) than with ramipril.

The results were very similar for the diabetic and non-diabetic subgroups [15]. Thus, we can conclude from ONTARGET that in people at high vascular risk, the effects of telmisartan on major renal outcomes are similar to ramipril. Although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes and should therefore not be recommended.

Very recently, the AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes) study [16] evaluated the renoprotective effects of dual blockade of the RAS by adding aliskiren, an oral direct renin inhibitor, to treatment with 100 mg daily losartan in 599 patients who had hypertension (135/78 mmHg) and type 2 diabetes with nephropathy. Treatment with 300 mg of aliskiren daily, as compared with placebo, reduced the mean urinary albumin-to-creatinine ratio by 20% (P < 0.001). Since a reduction of 50% or more was observed in 25% of the patients receiving the combination of both drugs, a considerable number of patients might have not responded to the renin inhibition [17]. Since only single BP and not 24-h BP measurements were done, it cannot be excluded that BP differences between the two treatment arms were more during daytime or night time [17]. Another critical point is the relatively poor glycaemic control (HbA1c 8.0 ± 1.5%) of the patients included in the AVOID study, and it remains unclear whether the effect of aliskiren would have been identical in patients receiving a more effective anti-diabetic therapy. Since the duration of the AVOID trial was relatively short, only 6 months, much longer studies over several years including ESRD as an end point are needed to confirm that the dual therapy to block the RAS with aliskiren and other agents will provide sustained renal protection and not cause an increased number of adverse events.

**Reduction of microalbuminuria reduces both the renal and cardiovascular risk**

Microalbuminuria in diabetic patients is a strong predictor for both diabetic nephropathy and cardiovascular disease. An observational follow-up study over 8 years in 216 type 2 diabetic patients with microalbuminuria from the Shiga University in Japan [18] investigated whether changes in microalbuminuria translate into changes in renal and cardiovascular risk. The patients were analysed according to diabetic nephropathy status in each 2-year follow-up period. Remission (50% reduction of microalbuminuria) was defined as a shift from microalbuminuria to normoalbuminuria, and progression was defined as shift into overt proteinuria. Two outcomes were assessed: (1) the first occurrence of a renal or cardiovascular event and (2) the kidney function as indicated by eGFR. Renal and cardiovascular events occurred in a total of 47 patients during the 8-year follow-up period. There were only 12 events (1 dialysis, 3 myocardial infarctions, 5 cases of angina,
1 worsening of congestive heart failure and 2 strokes) in the 50% reduction group ($n = 93$), in comparison with 35 events (3 dialyses, 5 myocardial infarctions, 7 cases angina, 2 worsening of congestive heart failure and 18 strokes) in the non-reduction group ($n = 123$). The 8-year cumulative incidence of evaluated events was significantly lower in the 50% reduction group than in the non-reduction group ($P = 0.0019$). A pooled logistic regression analysis revealed that the adjusted risk for events in subjects after a 50% reduction was 0.41 (95% CI 0.15–0.96).

In addition, the annual decline of eGFR in patients with a 50% reduction was significantly slower than in those without such a reduction ($-1.8 \text{mL/min per } 1.73 \text{m}^2/\text{year versus. } -3.1; P = 0.038$). Although these data provide strong clinical evidence implying that a reduction of microalbuminuria in type 2 diabetic patients is an integrated indicator for renal and cardiovascular risk reduction, much larger prospective clinical intervention studies are needed to improve both the renal and CVD morbidity/mortality in the large population of type 2 diabetic patients.

**Conflict of interest statement.** None declared.

**References**


15. Mann JF, Schmieder RE, McQueen M et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; 372: 547–553


Received for publication: 20.11.08
Accepted in revised form: 20.11.08