Angiotensin Blockade to Reduce Microvascular Damage in Diabetes Mellitus

Roland E. Schmieder, Stephan Martin, Gabriele E. Lang, Peter Bramlage, Michael Böhm

SUMMARY

Background: Diabetic retinopathy and microalbuminuria are often thought of as distinct disease entities despite their common pathophysiology. Many studies have addressed the prognostic significance of these conditions and their treatment.

Methods: Medline was selectively searched for articles published from 1948 to 2008 containing the terms “angiotensin,” “microalbuminuria,” and “retinopathy.” The results were further amplified by screening the reference sections of the retrieved articles.

Results: Diabetic retinopathy and microalbuminuria are expressions of microvascular damage. They are promoted by hypertension, hyperglycemia, dyslipidemia, and elevated levels of angiotensin II. They are treated by adjusting these risk factors to the near-normal range. In the IDNT study, angiotensin II blockade with irbesartan was found to lead to an absolute reduction of renal events by 7.4% as compared to standard treatment, and by 9.5% as compared to amlodipine. In the DIRECT study, candesartan reduced the progression of retinopathy by 13% and effected a regression by 34%. In the Steno-2 study, an intensive program of multifactorial risk reduction significantly lowered the rate of microvascular complications over a mean follow-up interval of 3.8 years. Over the longer term (13.3 years), this approach also led to a reduction of macrovascular events (HR 0.54 for mortality of all causes, 0.43 for cardiovascular mortality, and 0.41 for cardiovascular events).

Conclusions: Diabetic retinopathy and microalbuminuria are expressions of microvascular damage. They often appear together and point toward possible future macrovascular events. Multifactorial intervention can lessen the consequences of these pathological conditions.

Key words: diabetes mellitus, angiotensin blockade, microalbuminuria, retinopathy, cardiovascular risk

Although many type 2 diabetics die as a consequence of macrovascular events, the treatment of microvascular complications such as diabetic retinopathy and nephropathy is very significant in practice, as these conditions impair the quality of life and cause high costs. However, different organic manifestations are often diagnosed separately. There is not enough collaboration between the doctors and patients are not treated aggressively enough. In order to avoid vision loss and blindness, the German Society for Diabetes (Deutsche Diabetes Gesellschaft, DDG) recommends in their guidelines the interdisciplinary treatment of diabetic retinopathy and maculopathy by

- adjusting the blood sugar to a near normal range (see DDG Guideline "The Treatment of Diabetes mellitus type 1" and "Antihyperglycemic Treatment of Diabetes mellitus type 2") (e1, e2),
- normalization of blood pressure (see DDG Guideline "Management of Hypertension in patients with Diabetes mellitus") (e3),
- ophthalmological therapy.

Normal blood pressure (<140/85 mm Hg), near normal blood sugar (HbA1c <6.5%), as well as the adjustment of lipids (HDL cholesterol >1.1 mmol/L, triglycerides <1.7 mmol/L, total cholesterol <5.0 mmol/L) were important therapeutic pillars in the Steno-2 study. If accompanied by lifestyle modification, they significantly reduced microvascular complications after a mean monitoring period of 3.8 years (Figure 1) (3, 4). After 13.3 years, the number of macrovascular events (Figure 2) was significantly reduced (4). An increased angiotensin II concentration plays a special role, together with hypertension associated with diabetes and hyperglycemia. Angiotensin II leads to constriction of effenter arterioles in the kidney. It increases the filtration pressure in the glomerular capillaries and effects contraction of glomerular mesangium cells. This results in increased filtration of albumin into urine (e4). Furthermore, angiotensin II increases systemic blood pressure, leading to endothelial dysfunction and glomerular damage. In the retina, the renin-angiotensin system (RAS) is also activated in patients with diabetes. Angiotensin II is especially important for the following reasons (e5, 4): It mediates vascular growth and accelerates or causes development of proliferative retinopathy. Moreover, it increases permeability of retinal capillaries for high molecular substances and supports development of macular edema (e7).
The aim of the present study is to demonstrate the significance of retinopathy and microalbuminuria, as well as the significance of blockade of the activity of angiotensin II, and thus to blaze the trail for multifactorial therapy of microvascular diabetic modifications.

**Methods**

Medline was selectively searched for articles published from 1948 to 2008 containing the terms "angiotensin," "microalbuminuria," and "retinopathy" (English and German). The combination of "angiotensin + microalbuminuria" resulted in 786 hits. The combination of "angiotensin + retinopathy" resulted in 452 hits. The results were further amplified by screening the reference sections of the retrieved articles and selected according to relevance for the present review. Among them was a potentially relevant Cochrane review (e8).

**Microalbuminuria**

**Definition**

Increased excretion of albumin in urine is called microalbuminuria (Table). Thus, microalbuminuria marks the beginning of a progressive development which may lead to terminal renal failure and/or cardiovascular complications in the course of several years. If albumin is excreted below the threshold for microalbuminuria, the term “low-grade albuminuria” is used. This is also accompanied by an increased cardiovascular risk (5). According to the data of the Framingham study, an increased risk was detectable with >3.9 mg/g creatinine for men and >7.5 mg/g creatinine for women.

**Epidemiology**

The frequency of microalbuminuria in the population was 8.3% (6) in the NHANES III cohort (USA, 1988–94). In the PREVEND study, which was conducted in the Netherlands, it was 7.2% (7). In practices, the prevalence is clearly higher, due to several concomitant cardiovascular diseases:

- The prevalence is about 20% (8) in general medical care in Germany
- In practices specializing in diabetes at 39% (e9)
- In cardiological practices up to 58% (9).

In the context of these numbers, not enough tests for the appearance of microalbuminuria are performed in daily medical practice (8).

**Microalbuminuria and renal risk**

Patients with microalbuminuria have a 10- to 20-fold greater risk of developing manifest diabetic nephropathy (e10) in comparison to patients who do not excrete albumin. From then on, renal function decreases, with an observed annual loss of 3 to 5 mL/min under angiotensin blockade (instead of 12 mL/min without therapy). Meanwhile 30% to 40% of all dialysis patients in Germany suffer from renal insufficiency as a consequence of diabetes. The 5-year survival rate of diabetes patients with renal replacement therapy is 25% (e11).

**Possible interventions**

Several clinical studies have demonstrated the significance of blockade of the RAS for avoiding the progression of neural and retinal complications in patients with type 2 diabetes and microalbuminuria and blood pressure <140/85 mm Hg, near normal blood sugar with an HbA1c <6.5%, HDL cholesterol >1.1 mmol/L, triglycerides <1.7 mmol/L, and total cholesterol <5.0 mmol/L. OR, Odds Ratio; CI, confidence interval

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**TABLE**

| Classification of albumin elimination in urine (taken from [24]) |
|-------------------------|---------------------|---------------------|---------------------|---------------------|
| Urine collection method | Clearly normal | Low-grade albuminuria | Micro-albuminuria | Macro-albuminuria |
| 24 h collected urine    | < 6.7 mg/d    | 6.7–29.9 mg/d    | 30–299 mg/d    | ≥ 300 mg/d |
| Spontaneous urine, test strip | < 4.2 mg/L | 4.2–19.9 mg/L | 20–199 mg/L | ≥ 200 mg/L |
| Spontaneous urine, Albumin/Creatinine | < 3.9 mg/g (M) < 7.5 mg/g (W) | 3.9–16.9 mg/g (M) 7.5–24.9 mg/g (W) | 17–250 mg/g (M) 25–355 mg/g (W) | ≥ 250 mg/g ≤ 350 mg/g ≥ 300 mg/g |
| Practice orientated    | < 10 mg/g   | 10–29 mg/g     | 20–299 mg/g    | ≥ 300 mg/g |

M = men, W = women
renal insufficiency. In comparison to placebo, a decrease in the number of type 1 diabetics with doubling of serum creatinine was documented with captopril, by 48% (95% confidence interval [CI] 16–69) (e12). The patients had diabetic nephropathy (>500 mg protein excretion/24 h) and diabetic retinopathy. The primary combined endpoint of death, dialysis, and transplantation was reduced by 50% (95% CI 18–70).

There are already studies on patients with current diabetic nephropathy (10, 11) and on reducing the progression of microalbuminuria (12) for type 2 diabetes. These studies showed that blockade of the AT1 receptor is superior to standard therapy (without other RAS blocking substances) and to an amlopidine based regimen (absolute risk reduction over 2.6 years: 7.4% irbesartan versus standard therapy, 9.5% versus amlopidine based therapy [10]). The annual decrease in the glomerular filtration rate was less over longer treatment periods:

- IDNT (10), period: 2.6 years, decrease: 5.5 mL/min/1.73 m²/year
- RENAAL (11), 3.4 years, decrease: 4.4 mL/min/1.73 m²/year
- DETAIL (13), 5 years, decrease: 3.7 mL/min/1.73 m²/year

These effects are not only the result of blood pressure management, as the example of the analysis in the IDNT study showed (e13). In every quartile of the systolic blood pressure, the effects of RAS blockade were greater than those with placebo or those with calcium antagonists.

In the context of diabetic nephropathy, combinations of RAS blockers for reducing protein are effective and can still be employed according to the results of the ONTARGET study (13, e14). As an alternative, higher dosages of an AT1 blocker can be used. Dosages up to 128 mg candesartan were successfully tested in the studies of Schmieder et al. (14) and Burgess et al. (e16).

**Retinopathy**

**Definition**

Diabetic retinopathy is evoked by microangiopathy. It causes decreased visual acuity, a restricted visual field and can subsequently lead to blindness. The clinical differentiation is made between non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) and diabetic macular edema (e18).

NPDR is marked by vascular modifications, such as micro-aneurysms, blot hemorrhages, and cotton wool spots. Progression of the disease leads to perfusion of retinal capillaries: The tissue of the retina becomes ischemic. This leads to venous capillary and to intraretinal microvascular modifications, to further bleeding, and to exsudation. Proliferative diabetic retinopathy (PDR) is characterized by neovascularization. Formation of new blood vessels is often accompanied by areas of bleeding in the vitreous body and sometimes by detachment of the retina. If neovascularization extends into the area of the anterior segment of the eye, newly formed vessels of the iris can close the chamber angle. This results in the development of glaucoma. Diabetic macular edema (DMO) is marked by the breakdown of the blood-retina barrier with increased vascular permeability and is accompanied by retinal edema and hard exudates.

**Epidemiology**

Diabetes is the most common cause of blindness in patients of working age. In the USA, about 3.6% of patients with type 1 diabetes and 1.6% of patients with type 2 diabetes are affected by this. In England and Wales, about 1000 patients become blind each year from diabetes (e19). The prevalence of diabetic retinopathy is between 0% and 3% in type 1 diabetics at the time of the diagnosis of diabetes. The prevalence in type 2 diabetes is between 6.7 and 30.2%. The prevalence and the severity of diabetic retinopathy particularly increase with the duration of diabetes (e20).

**Retinopathy and blindness**

Most of the patients with type 1 diabetes and more than 60% of the patients with type 2 diabetes who have had the disease for 20 years develop diabetic retinopathy (e21). This is linked to a clear reduction in
the quality of life. In a study of Brown et al., patients stated that they would be willing to swap (e22) 40% of their remaining life span for elimination of ocular disease.

**Possible interventions**

There are many clinical studies in which the significance of blockade of the renin-angiotensin system (RAS) (*Figure 4*) for the prevention and treatment of diabetic retinopathy was examined. This includes three smaller studies (e23–e25), as well as the EUCLID study (16). EUCLID compared the ACE inhibitor lisinopril with placebo in 530 patients with type 1 diabetes (16). The probability ratio for the progression of retinopathy was 0.5 under lisinopril in comparison to placebo. However, at the start of the study, the HbA1c values in the lisinopril group were 0.4% less than in the control group and this led to a slightly greater decrease in blood pressure under the ACE inhibitor (3 mm Hg).

A multicenter study over a period of 5 years with 11,140 patients with type 2 diabetes (ADVANCE) examined the significance of a decrease in blood pressure and strict control of blood sugar on macrovascular events (17). One of the secondary target parameters was the reoccurrence or the deterioration of diabetic retinopathy. There were no significant differences between patients who were treated with perindopril/indapamide and the control group. Possible explanations could be...
based on the high proportions of unblinded medication with perindopril, even in the placebo group (55%), and the intensive insulin and statin therapy. Detailed analyses are expected from the sub-study Advance Retinopathy Measurements (AdRem) (e26).

In the DIRECT study (15), the angiotensin receptor blocker candesartan was used at a dosage of up to 32 mg, to guarantee maximal blockade of the retinal RAS (Figure 5). In the DIRECT-Prevent 1 trial (18), the incidence of diabetic retinopathy in type 1 diabetes was examined (blood pressure at the start of the study: 116/72 mm Hg). Two or more steps progression (ET-DRS scale) was used and a trend (–18%; p = 0.0508) was shown. With three or more steps, the incidence was significantly reduced by 35% (p = 0.003).

However, in the DIRECT-Protect 1 trial (18), the progression in type 1 diabetes was examined (49% of the patients had only micro-aneurysms). Only nominal changes were found for the progression and regression of three or more steps on the ETDRS scale. In DIRECT-Protect 2 (19), the progression of retinopathy in type 2 diabetes was examined. At the beginning, 29% of the patients had only micro-aneurysms in the worse eye, 54% mild non-proliferative diabetic retinopathy and 17% moderate NPDR. After a median follow-up of 4.7 years, retinopathy had improved to a greater extent in patients receiving 32 mg candesartan than in those receiving placebo (p = 0.003). However, the progression (three or more steps on the ETDRS scale) was decreased by 13% (p = not significant). In contrast, regression (three or more steps on the ETDRS scale) was relatively increased by 34% (p = 0.009).

In exploratory analyses, the results of the DIRECT study were adjusted for various factors, including blood pressure (about 2 to 3 mm Hg in favor of candesartan). In all cases, the effects on diabetic retinopathy were robust, i.e., the effect sizes and p-values after adjustment only changed quantitatively but not qualitatively.

**Macrovascular prognosis with microalbuminuria and retinopathy**

The detection of microalbuminuria and retinopathy does not only indicate an increased risk in patients for the development of proliferative diabetic retinopathy and nephropathy. The association of these risk factors with cardiovascular events has also been described in studies.

**Microalbuminuria**

There is a positive clinical correlation between the extent of albumin excretion and cardiovascular events. The adjusted relative risk of macrovascular events in the MICRO-HOPE study was clearly increased when microalbuminuria was present (relative risk [RR]: 1.83), as well as the total mortality (RR: 2.09) and admissions to hospital because of heart failure (RR: 3.23) (e27). The one-year mortality was increased by the factor of 3.4 to 5.0 after cardiac infarction and the presence of microalbuminuria, at a threshold of 50 mg albumin/g creatinine on the first day after the event (e28).

In an analysis of the LIFE study (e29), the patients were classified into four groups by the rate of albumin excretion at the start of the therapy and after one year of observation. Additionally, the incidence of the combined endpoint of cardiovascular death, non-fatal stroke, and myocardial infarction was evaluated. Patients under treatment with AT1 blockers exhibited a disproportionate reduction in albuminuria and had clearly fewer cardiovascular events (1.8% or 3.4%) than patients with smaller changes in albuminuria (2.7% or 6.1%; p<0.001).
Retinopathy

Retinopathy is a marker for an increased cardiovascular risk. In a cohort of 2103 type 2 diabetics without previous cardiovascular events, 406 (19.3%) developed such an event in the following 7 years (e30). With a hazard ratio (HR) of 1.61 for NPDR and 3.75 for PDR, the risk for men was also increased after multiple adjustment for classical risk factors (women: HR = 1.67 for NPDR and HR = 3.81 for PDR). When the risk factors were adjusted for the presence of hypertension and advanced nephropathy, the increase in risk for NPDR lost its significance.

In a cohort of 11 612 persons, Wong et al. examined whether diabetic retinopathy is a pathogenic factor for the development of heart failure (e31). The incidence in patients with retinopathy was 15.1% after 7 years and 4.8% in the control group (p<0.001). Even after adjusting for the known risk factors, the relative risk was still 1.96.

Comorbidity of microalbuminuria and retinopathy

The diagnosis of diabetic nephropathy is supported by simultaneous diagnosis of retinopathy (20, 21). With young type 1 diabetics, there is no initial connection between the appearance of microalbuminuria or retinopathy and changes in coronary perfusion (e32). However, over a period of 12 years, microalbuminuria and retinopathy were linked with the development of cardiac disease (e33).

In a group of 4416 type 2 diabetics, Tong et al. examined how the diagnosis of retinopathy, as well as of micro- or macroalbuminuria, affects vascular events (22). If retinopathy was present, the risk was only slightly increased—with a hazard ratio (HR) of 1.61—but increased more when accompanied by microalbuminuria (HR: 2.59) or macroalbuminuria (HR: 6.83). HR for microalbuminuria alone was 1.93 and for macroalbuminuria 4.34. Ioannidis et al. pursued the question as to whether an examination of the eyes and the excretion of albumin in urine could be a simple screening measure to increase the accuracy of cardiac SPECT examination. The answer is yes. Patients with microalbuminuria and retinopathy had a positive scan in 94% of cases (n = 15 of 16) and 83% of all patients (n = 30 of 36) with a negative scan showed neither microalbuminuria nor retinopathy (23).

Conflict of interest statement

Professor Martin is the national coordinator of the DIRECT study and member of the national and international Advisory Board of the DIRECT study. The DIRECT study was financed by the companies Takeda, and AstraZeneca. Dr. Bramlage PD was financially supported for research work and lectures by the companies Sanofi-Aventis, Takeda, Daiichi Sankyo, Novartis, Berlin-Chemie, Schwarz Pharma, and Medac. Professor Böhm received support for research and payment for lectures from the companies Boehringer Ingelheim, and Sanofi-Aventis. Professor Schmieder received support for research and payment for lectures from the companies AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Sanofi-Aventis, and Takeda. Professor Lang declares that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

REFERENCES


Key messages

- Diabetic retinopathy and microalbuminuria are expressions of microvascular damage.
- Blood sugar, lipids, and blood pressure must be adjusted to within a near normal range, preferably with ACE inhibitors or AT1 blockers.
- Adjusting these risk factors to a near normal range decreases additional microvascular complications and in the long-term reduces cardiovascular morbidity and mortality.
- Interdisciplinary collaboration between diabetologists, nephrologists, cardiologists and ophthalmologists, as well as general practitioners and internists seems to be necessary for these diseases.


Corresponding author
Prof. Dr. Roland E. Schmieder
Nephrologie und Hypertensiologie
Universitätsklinikum Erlangen
Krankenhausstr. 12
91054 Erlangen, Germany
roland.schmieder@uk-erlangen.de

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