REVIEW ARTICLE

Angiotensin Blockade to Reduce Microvascular Damage in Diabetes Mellitus

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

Medizinische Klinik 4,
Nephrologie und Hy-
pertensiologie, Univer-
sitätsklinikum Erlan-
gen: Prof. Dr. med
Schmieder

Westdeutsches Diabe-
tes- und Gesundheits-
zentrum, Sana Kliniken
Düsseldorf: Prof. Dr.
med. Martin

Augenklinik, Univer-
sitätsklinikum Ulm:
Prof. Dr. med. Lang

Institut für Kardiovas-
kuläre Pharmakologie
und Epidemiologie,
Mahlow: PD Dr. med.
Bramlage

Klinik für Innere Medi-
zin III (Kardiologie, An-
giologie und internisti-
sche Intensivmedizin),
Universitätsklinikum
des Saarlandes, Hom-
burg/Saar: Prof. Dr.
med. 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 (hazard ratios for different complications varying from 0.27 to 0.45). 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 (1). 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 (2)

- 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 efferent 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).

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FIGURE 1

Risk reduction of microvascular changes in the Steno 2 study (3) after 3.8 years on the basis of a standard therapy orientated on the guidelines in comparison to intensified therapy, 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

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

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
Practice orientated	< 10 mg/g	10–29 mg/g	30–299 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) (e 12). 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 amlodipine based regimen (absolute risk reduction over 2.6 years: 7.4% irbesartan versus standard therapy, 9.5 % versus amlodipine 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 exudation. 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

FIGURE 2

Cumulative incidence of cardiovascular events and death from cardiovascular causes such as non-fatal stroke, non-fatal myocardial infarction, coronary bypass surgery, percutaneous coronary intervention, revascularization and amputation, in the Steno 2 study (4). Comparison between conventional standard therapy orientated on the guidelines and intensified therapy in patients with type 2 diabetes and microalbuminuria and blood pressure <140/85 mm Hg, near normal blood sugar with HbA1c <6.5%, HDL cholesterol >1.1 mmol/L, triglycerides <1.7 mmol/L, and total cholesterol <5.0 mmol/L.

(DMO) is marked by the breakdown of the blood-retina barrier with increased vascular permeability and is accompanied by retinal edema and hard exudates.

Modifications of the retina are measured by the so-called ETDRS (Early Treatment of Diabetic Retinopathy Study) scale (e17, 16), which is based on the Airlie House Classification of Diabetic Retinopathy (15) (Figure 3).

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

Severity of diabetic retinopathy.

a) Ocular fundus of a patient with incipient non-proliferative diabetic retinopathy (ETDRS-Score 20/20).

b) The ETDRS-Score is calculated by considering 7 defined fields of the ocular fundus and is transferred into the scale below.

Besides, the figure shows a comparison between clinical stages with steps of this scale. NPDR, non-proliferative diabetic retinopathy, PDR, proliferative diabetic retinopathy, ETDRS, Early Treatment of Diabetic Retinopathy Study

FIGURE 3

a Right eye, grade 20

b Left eye, grade 20

Micro-aneurysms

None

Mild NPDR

Moderate/severe NPDR

Mild PDR

High risk PDR

Advanced PDR

Only micro-aneurysms

Moderate NPDR

Severe/very severe NPDR

Moderate PDR

High risk PDR

Advanced PDR

10 20 35 43 47 53A-D 61 65 71 75 81 85
53E

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

FIGURE 5

Odds ratio for progression of retinopathy. Overview of the results of the studies of Larsen et al., Chase et al., Ravid et al., and the EUCLID-, ADVANCE- and DIRECT studies. ETDRS, Early Treatment of Diabetic Retinopathy Study Scale (15–19, e23–e26)

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.

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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.

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

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