tempting to speculate that there may exist a vicious circle between adiponectin and insulin resistance (Figure 12). Low adiponectin levels might thus contribute to insulin resistance to some extend, the resulting hyperinsulinemia further lowers adiponectin levels. However, this appears to be relevant only up to a certain threshold, as adiponectin KO-mice do not display an extensive degree of insulin resistance. Still this effect may contribute to the increased cardiovascular risk of insulin resistant individuals.

3. Cytokines and diabetic retinopathy

3.1 Introduction

Recent estimates suggest about sixteen million individuals having diabetes mellitus, 50% of them being unaware of their disease (100). A considerable amount of patients present with vascular complications already at time of diagnosis (101). Diabetes mellitus is associated with various functional and morphological vascular alterations, some of them leading to severe complications of the eye, kidney, nerves and the heart.

The most frequent vascular complication of type 1 diabetes is diabetic retinopathy. Together with macula degeneration, it is the major cause of blindness in industrial nations (102).

Loss of pericytes is an early event in diabetic retinopathy and appears to be related to the angiopoetin system (103, 104). Clinically microaneurysms are among the early signs of diabetic retinopathy. Microaneurysms for themselves appear to have no apparent clinical impact, except the fact that they are predictive markers of the

progression of diabetic retinopathy. There is an almost linear increase of risk of progressive retinopathy with increasing number of retinal microaneurysms (105). When a critical level of ischemia is reached, a clinically relevant angiogenic response occurs with a dramatically increased risk of vitreous haemorrhage or retinal detachment, finally causing loss of vision.

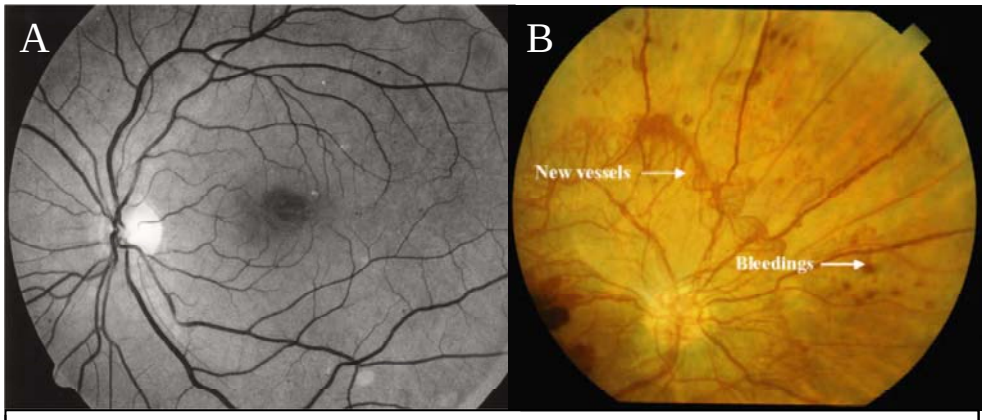

Figure 13: Fundus photographie of a healthy individual (A: courtesy from Dr. Meyer-Schwickerath, Bochum) and an individual with proliferative diabetic retinopathy characterised by retinal angiogenesis and intraocular haemorrhage. (B: Courtesy from Dr. Heimann, Department of Ophthalmology, Charité Berlin)

Blindness is about 25 times more common in individuals with diabetes compared to those without. The socio-economic impact of these data is dramatic. About 5000 new cases of blindness occur each year in the United States as a result of diabetic retinopathy (102). Computer simulations resulted in estimates that appropriate treatment of type 1 diabetes would save about $101 million and 47,374 person-years of sight annually and $247.9 million and 53,986 person-years of sight for patients with type 2 diabetes at current treatment level (106, 107).

While it is still under debate, whether the risk for atherosclerosis and coronary heart disease is increased due to impaired glucose metabolism alone, there is clear evidence that microvascular complications such as retinopathy strongly depend on

glucose control. The major current hypotheses explaining the mechanisms by which hyperglycaemia is linked to tissue damage are (108):

-accumulation of polyol in the respective tissues

-increase of intracellular N-acetylglucosamine by shunting of glucose through the hexosamine pathway

-activation of protein kinase C (PKC)

-increase of advanced glycation end products (AGEs)

-oxidative stress.

These proposed mechanisms are not mutually exclusive and there is evidence that some of them overlap considerably.

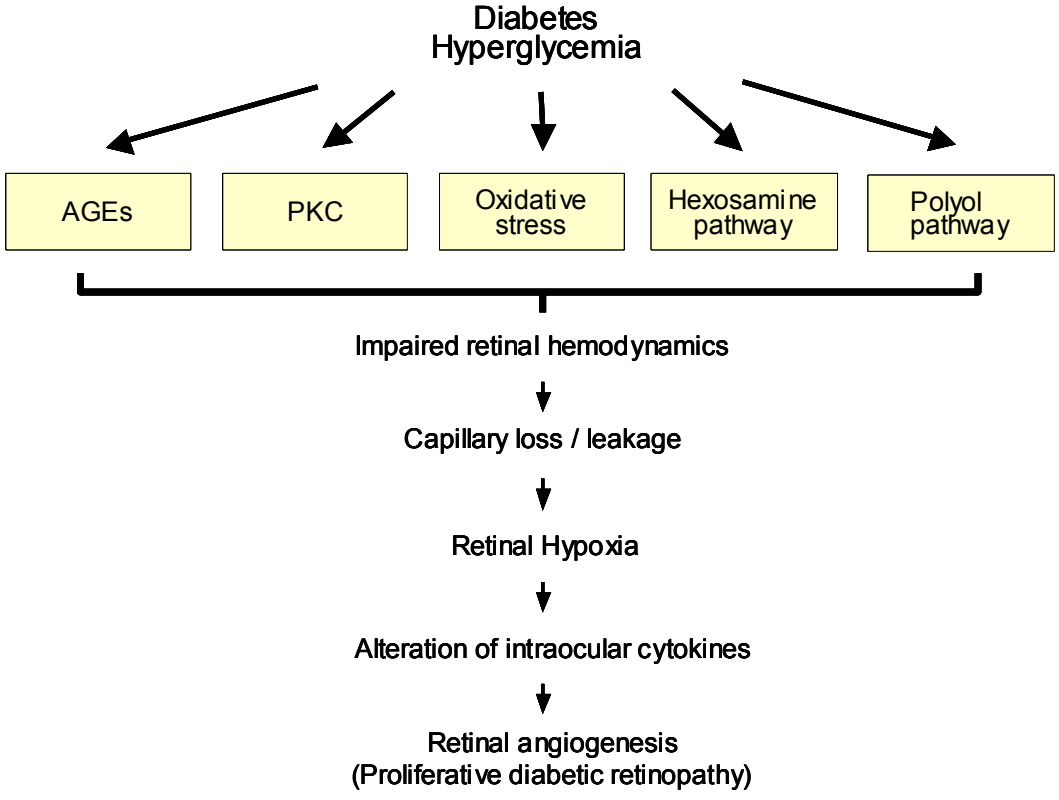

Figure 14: Scheme of the current biochemical hypothesis in the pathogenesis of microvascular diabetic complications

There is little doubt that these changes occur early in the time course of microvascular complications, while changes in cytokines are relatively late events. Nevertheless some central morphological and functional changes finally depend on those cytokine changes and make them a potential therapeutic target and a relevant interesting focus of research.

3.2 Cytokines as a common final pathway to diabetic retinopathy

The aforementioned biochemical pathways have in common that they finally change the expression or functional properties of cytokines, matrix components or other effectors at the protein level. There has been considerable work to understand which cytokines are involved in the development of microvascular complication, to understand the mechanisms of these cytokines and to investigate inhibitors of the signaling pathways involved.

The cytokine alterations induce the typical morphological pattern of diabetic complications, such as retinal neovascularization in proliferative diabetic retinopathy (PDR) (109). In the healthy eye the occurrence of angiogenesis is under tight regulation of both activator and inhibitor molecules. Vascular blood supply is essential in the retina, but tissues such as the cornea and vitreous do not require a vascular system and are therefore free of vessels. This avascularity implies the existence of anti-angiogenic factors. Under physiological conditions, the inhibitors predominate, thereby preventing growth. The switch to angiogenic retinopathy depends on both, up-regulation of angiogenic stimulators (i.e. vascular endothelial growth factor, insulin-like growth factors) and down-regulation of angiogenesis inhibitors (i.e. pigment epithelium derived factor, angiostatin) (110, 111). Concomitantly inhibition of angiogenic cytokines such as VEGF as well as

replenishment of angiogenesis inhibitors such as PEDF provide interesting new therapeutic approaches.

3.2.1 Vascular Endothelial Growth Factor

VEGF is an endothelial-specific mitogen as well as an angiogenic cytokine. It is thought to be the main stimulator of angiogenesis (112) and is characterised by its growth-promoting ability as well as its potent permeability-inducing effects (113). In the presence of VEGF, endothelial cells are stimulated to degrade their basement membrane and to migrate with concurrent release of matrix metalloproteases (MMPs) and expression of integrins. Additionally, VEGF is capable of stimulating endothelial cells to proliferate and to survive (114). Hypoxia is an important regulator of angiogenesis. Numerous studies have revealed the induction of VEGF expression under hypoxic conditions (114-116). This process is mediated by up-regulation of hypoxia-inducible factor (HIF)-1α, which binds to the VEGF promoter and initiates its transcription (114). Because VEGF is a diffusible and is an oxygen regulated angiogenic factor it has been concluded that VEGF is a potential mediator of intraocular neovascularization. In the eye, neovascular activity has been postulated to be produced by the retina and to be diffusible since extensive retinal non-perfusion results in angiogenesis as far anterior as on the iris, which is called rubeosis iridis. The ability to monitor and to grade neovascularization within the eye by funduscopy combined with the ability to aspirate vitreous fluid makes the eye an ideal setting to investigate the development of angiogenesis in vivo in man. We thus compared vitreal levels of various angiogenic and anti-angiogenic cytokines in control individuals, patients with proliferative diabetic retinopathy and those with massive neovascularization due to non-diabetic disease such as central vein occlusion.

Control individuals were those, who required vitrectomy to any ophthalmologic indication (i.e. accidents), but had no proliferative eye disease. With respect to VEGF, indeed increased levels of VEGF were found in the vitreous (Figure 15) and the retina of patients and laboratory animals with ischemic retinopathies (111, 117-119). These data clearly support the concept, that VEGF is a major mediator of angiogenic response in hypoxic eye disease in humans.

Confirmation of its critical role in retinal neovascularization was given by the ability of VEGF antagonists to suppress the growth of blood vessels in animal models (120, 121). Some VEGF antagonists are currently undergoing clinical studies to test its therapeutic benefits in proliferative eye diseases (see also Table 10).

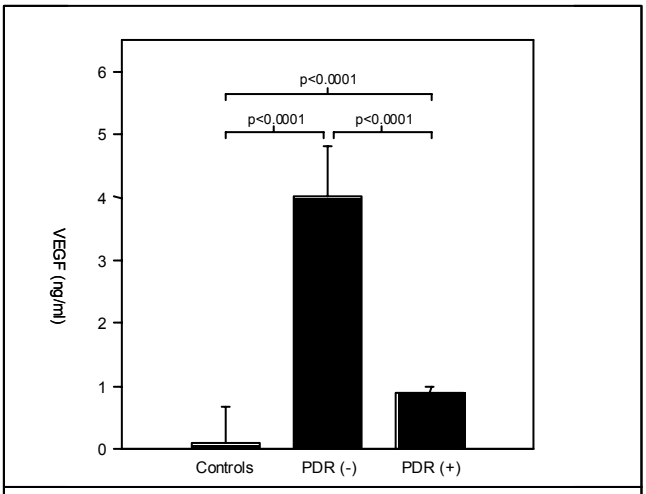

Figure 15: Levels of vitreal VEGF depend upon previous photocoagulation. PDR (-) are patients with PDR without prior photocoagulation; PDR(+) are patients with PDR with prior photocoagulation

In summary, we (111) and others have shown that VEGF is elevated in the vitreous of patients with proliferative diabetic retinopathy compared to individuals without

proliferative eye disease. These data further suggest, that VEGF is involved in the pathogenesis of proliferative diabetic retinopathy in humans.

3.2.2 Pigment Epithelium Derived Factor (PEDF)

Several naturally occurring inhibitors of angiogenesis have been identified, including PEDF, endostatin and angiostatin. PEDF is the most potent inhibitor of angiogenesis in the eye (122). Besides its anti-angiogenic effects, PEDF was shown to be neuroprotective and might be involved in neuronal differentiation in the retina (123). Tombran-Tink and associates were the first who isolated PEDF from medium conditioned by human fetal RPE cells (124). PEDF acts via induction of apoptosis in endothelial cells that are forming new vessels (125), whereas the neuronal survival might be promoted through PEDF-induced activation of NF-κB (126). Its production by retinal cells is positively correlated with oxygen concentrations, implicating its loss in ischemia-driven neovascularization in the retina (127). Gao and colleagues demonstrated an increased VEGF/PEDF ratio in the retina of rats with ischemia-induced neovascularization, and thus suggested that the imbalance between angiogenic stimulators and inhibitors may contribute the development of retinopathy (128).
In animal models, systemically or intravitreal administered PEDF was able to block neovascularization in ischemia-induced angiogenesis (122, 129). We and others have demonstrated that vitreous and retinal levels of PEDF are decreased in diabetic patients with proliferative diabetic retinopathy (110, 130), while PEDF levels appear to be unchanged in patients with diabetes mellitus, but without ocular changes (unpublished data). The question of retinal expression of PEDF was addressed in immunohistochemical studies. While a relatively high expression of PEDF was found in the retina of healthy controls, a substantial reduction was found in eyes from

individuals with proliferative diabetic retinopathy. Accordingly to the above mentioned data of unchanged vitreous levels in individuals with diabetes but without ocular changes, immunohistochemistry was also not indicative of substantial changes in patients with NPDR (Figure 16).

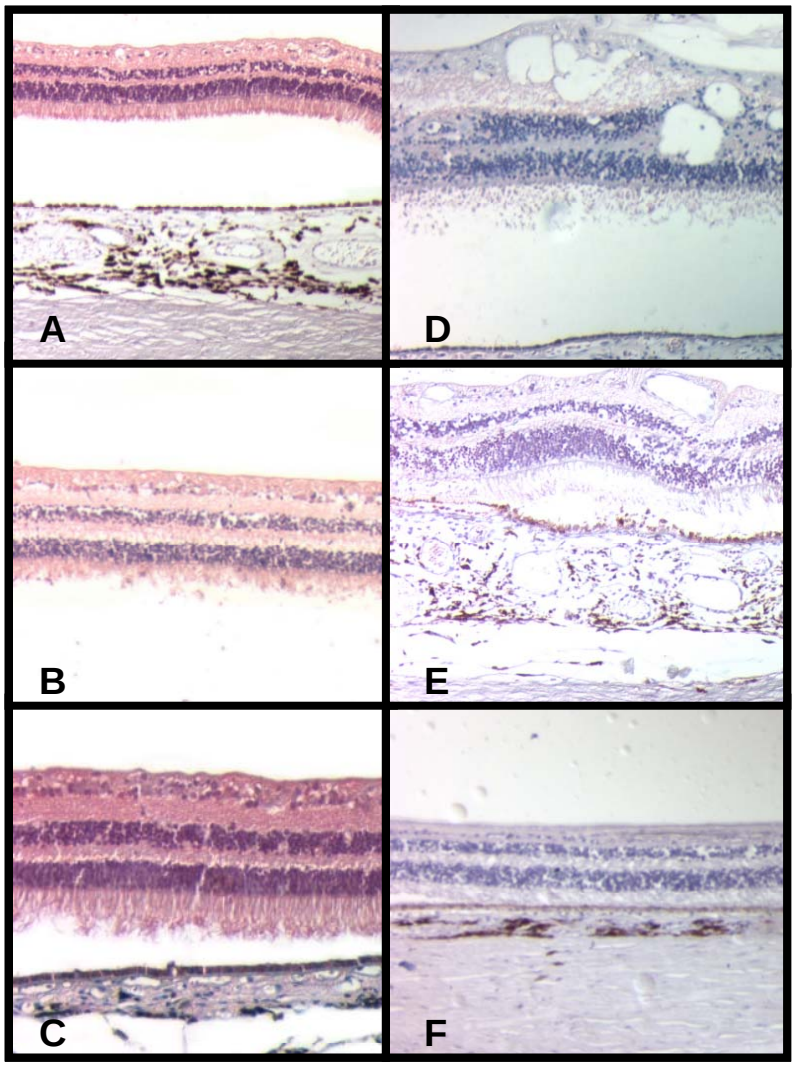

Figure 16: Immunohistochemistry using a polyclonal PEDF antibody. Increased PEDF-specific staining intensity in controls (A), patients with diabetes without ocular abnormalities (B) and patients with NPDR (C) compared to patients with PDR (D) and patients with quiescent PDR after retinal photocoagulation (E). Specificity of reaction was demonstrated by absence of staining after incubating sections with the primary antibody after preabsorption with the recombinant antigen (F).

The immunohistochemical results were basically reflected in the vitreal PEDF levels with control individuals having the highest levels and individuals with PEDF having substantially reduced levels. Interestingly we found a strong correlation of PEDF levels with localization of angiogenesis (Figure 17) and intraocular neovascular activity (Figure 18). Those individuals with extensive neovascularization (NVE and NVD) had the lowest levels, comparable to those with an active retinal neovascularization.

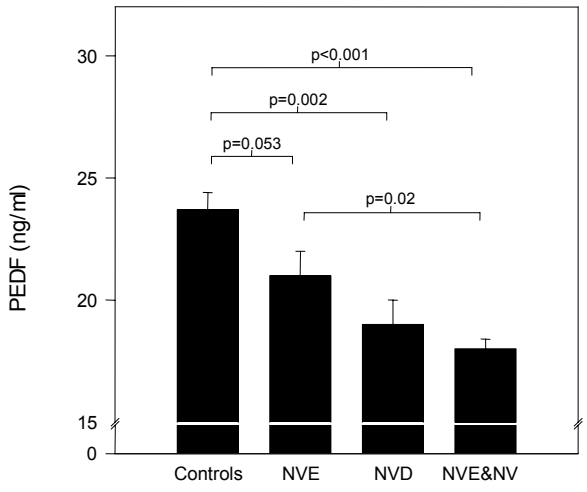

Figure 17: Concentrations of PEDF in human vitreous depending upon localization of neovasularization. Patients with new vessels on the disc (NVD), new vessels elsewhere (NVE) and patients with both, NVE and NVD, were compared.

Interestingly, Boehm and co-workers demonstrated that VEGF levels in the aqueous humour are increased in both diabetic patients with and without proliferative retinopathy compared to non-diabetic controls, whereas PEDF levels are only decreased in diabetic patients with proliferative retinopathy (131). The same group found that the endogenous content of PEDF in aqueous humour predicted pro-

gression of diabetic retinopathy, whereas VEGF content had no predictive quality (131).

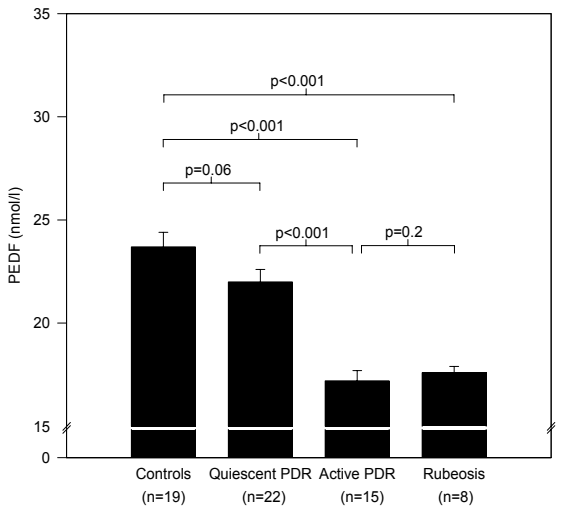

Figure 18: Concentrations of PEDF in human vitreous depending upon activity of retinal neovascularization. Controls without angiogenesis, patients with quiescent PDR, patients with active PDR and non-diabetic patients with extensive retinal neovascularization due to central vein occlusion (Rubeosis) were compared.

Because of its efficient anti-angiogenic properties, PEDF has been proposed to be successful in the therapy of retinopathy, either delivered systemically, locally or in gene therapy.

In summary, our data strongly support the concept that PEDF is a protective factor in healthy eye, which is lost in diabetic retinopathy and other hypoxia driven proliferative eye disease (110).

3.2.3 Insulin like growth factors (IGFs)

IGF-I was shown to act directly as an angiogenic factor. Furthermore it was proposed to influence VEGF gene expression (132), thus acting as a permissive factor for maximum VEGF stimulation in angiogenesis (133). Only a small amount of IGF-I is circulating in the active free form, the greater part is bound to one of the six IGF binding proteins (IGFBPs), which are, among others, capable of modulating the bioavailability of IGF-I at target cells. It has been suggested that growth hormone (GH) and IGF-I play a key role in the progression of diabetic retinopathy, after Poulsen observed regression of diabetic retinopathy (DR) after postpartal infarction of the pituitary in Sheehan's syndrome (134). Subsequently, hypophysectomy appeared as an effective therapy of proliferative diabetic retinopathy (PDR), as it was shown by Poulsen (1966), Deckert (1967) and Sharp (1987) (135-137). Similarly, diabetic dwarfs with low IGF-I serum levels due to a GH deficiency showed a reduced incidence of PDR compared to diabetic patients (138, 139).

Correspondingly, in states of elevated IGF-I levels such as pregnancy and puberty, a progression of retinopathy was demonstrated (140-142). Various studies demonstrated elevated intraocular levels of IGF in patients with diabetic retinopathy compared to controls (143-146). Simo and co-workers demonstrated elevated levels of vitreal free IGF-I levels, if no adjustment for total intravitreal protein concentration was performed (147). With respect to therapeutic approaches based on systemic IGF-I lowering, the source of elevated intraocular IGF-I levels is of major importance. In the recent years some doubts about the strong association between circulating IGF-I and proliferative retinopathy arose. Several studies revealed controversial results with respect to the association between systemic IGF-I and diabetic retinopathy (148-152). However, elevated intraocular levels might result from

elevated systemic levels, from a progressive breakdown of the blood-retina barrier and from an increased intraocular production of IGF-I. This question has been addressed by our study investigating the origin of increased intraocular IGF-I levels *in vivo* in proliferative diabetic retinopathy by measuring parallely serum and vitreous levels of IGF´s and the extraocularly synthesized protein albumin as a permeability marker (145).

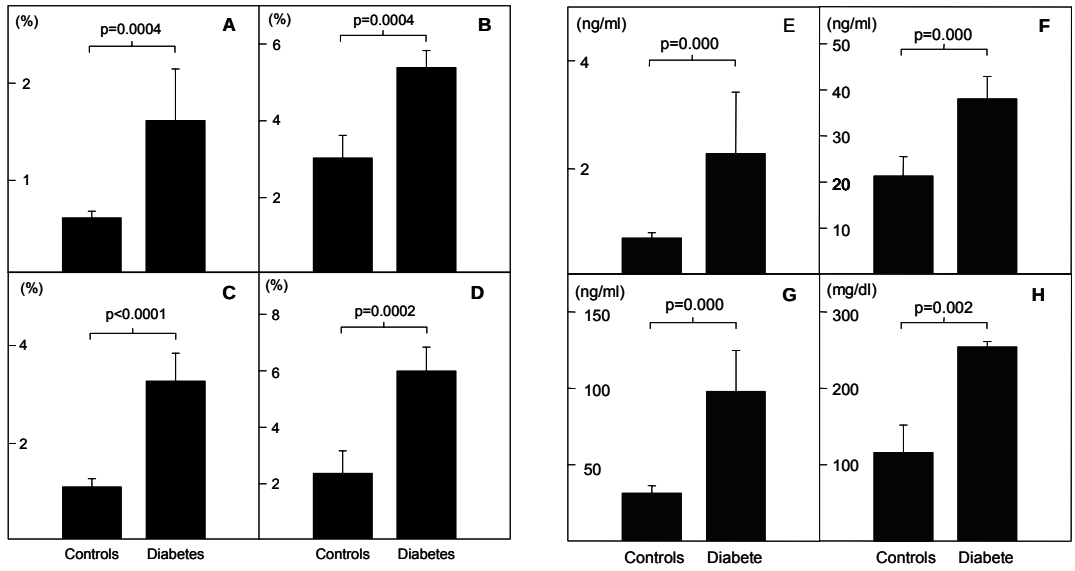

Figure 19: Increased levels of (A) IGF-I, (B) IGF-II, (C) IGF-BP3 and (D) albumin in human vitreous of patients with proliferative diabetic retinopathy compared to controls. Elevations of the mean vitreal concentrations calculated as percentage of the individual serum level in patients with proliferative diabetic retinopathy compared to controls regarding IGF-I (E), -II (F), IGF-BP3 (G) and the permeability marker albumin (H).

This study demonstrated that the increase of the angiogenic growth factor IGF-I (2.64-fold) is quantitatively comparable to the elevation of the permeability marker albumin (2.5-fold) in the diabetes group. Additionally a significant correlation between intraocular albumin and IGF-I levels calculated as percentage of the individual serum levels could be demonstrated. Thus the increase of intraocular IGF´s appears to be

primarily due to a spill-over of serum protein, although a local production of IGF-I has been established by demonstration of its mRNA in the retina.

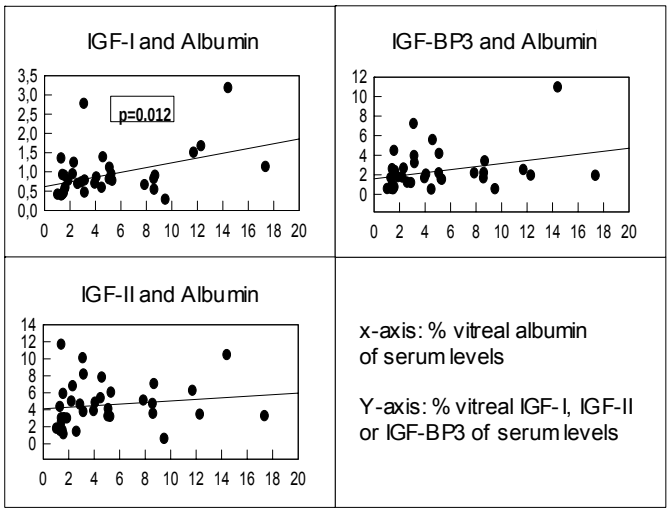

Figure 20: Significant correlation between intraocular albumin and IGF-I levels calculated as percentage of the individual serum levels (r=0.42; p=0.012).

However, mRNA levels were even decreased in diabetes, despite the various reports on elevated vitreal levels (153). Given the above mentioned data, there is little doubt that the major part of vitreal IGF-I appears to result from serum-overflow, although the amount of the locally synthesized IGF-I is difficult to estimate. The influx of serum proteins appears to be determined by an increased permeability of the blood-retina-barrier in PDR to intermediate-sized proteins rather than from a generalized breakdown or vitreal haemorrhage with overflow of large sized proteins such as alpha$_2$-macroglobulin (145).

From therapeutic point of view a specific time window directly after substantial improvement of metabolic control appears to be of special interest. A rapidly improved glycaemic control is frequently associated with worsening of diabetic retinopathy, probably due to the initial elevation of IGF-I levels (154-156). This rapid

progression of diabetic retinopathy occurs immediately after improving metabolic control and was reported to be temporary (156). This phenomenon may be of clinical relevance. Thus the inhibition of IGF-I with somatostatin analogues appears to be a promising therapeutic approach for patients with PDR and improvement of metabolic control. In addition, a combined treatment with IGF-I/GH inhibitors and photocoagulation might be a successful therapy for PDR, since it was shown that after retinal scatter photocoagulation, VEGF levels were dramatically reduced, whereas the levels of IGF-I were not changed (146). In clear contrast some authors postulate a benefit of IGF-I supplementation instead of its suppression in diabetic patients (157). Exemplarily it was reported that co-therapy with IGF-I and insulin for 12 weeks is a more efficient therapy for the improvement of glycaemic control in type 1 diabetes than insulin treatment alone (158). However, 8% of the patients had a significant worsening of retinopathy despite the short period of therapy. Thrailkill and associates suggested the progression of retinopathy to be dose-related, because most of these patients received the two highest doses of IGF-I (158). There are great concerns about IGF-I related ophthalmologic changes after all. The worsening of retinopathy might be also associated with long-term therapy at the lowest IGF-I doses, so the safety of co-therapy with IGF-I and insulin has to be carefully investigated before using it as new treatment in patients with type 1 diabetes (159).

In summary, we have demonstrated that the major part of intraocular IGFs derives from circulation in vivo in man, although it is not excluded that small amounts might still be produced locally (145). These data tentatively suggest that systemic IGF-lowering therapy might be helpful to prevent progression of diabetic retinopathy.

3.3 Photocoagulation induced changes of intraocular cytokines

Retinal scatter photocoagulation is the standard therapy in proliferative diabetic retinopathy and often prevents further retinal neovascularization. It has been shown to be associated with a reduction in the incidence of severe visual loss and retinal neovascularization (160). Despite these clear effects, the molecular mechanisms of the angiogenesis inhibitory effects of retinal photocoagulation are still unclear. The switch to an angiogenic phenotype of tumours requires both up-regulation of angiogenic stimulators and down-regulation of angiogenesis inhibitors. Vice versa anti-angiogenic effects of retinal photocoagulation might be mediated by an increased expression of an angiogenesis inhibitor or down-regulation of angiogenic growth factors such as VEGF or IGFs. The first publication on a post-photocoagulation levels of VEGF in the vitreous demonstrated reduced levels of VEGF after retinal photocoagulation in 6 patients, thus indicating that a reduced expression of angiogenic growth factors might be responsible for the positive therapeutic effects (117). However, the number of patients with subsequent measurement of VEGF was small in this study and vitreous was re-examined for VEGF after dilution of the vitreous in the first vitrectomy (117). In a subsequent study we were able to demonstrate in a sufficiently large cohort that VEGF is substantially reduced in patients with proliferative diabetic retinopathy with prior photocoagulation compared with those without previous treatment (111) (Figure 15).

As mentioned above, positive effects of retinal photocoagulation might also be mediated by an increased expression of angiogenesis inhibitors. We and others have shown that patients with previous photocoagulation have a replenishment of intraocular PEDF, which might also participate in a reduced neovascular activity compared to patients without prior photocoagulation (110, 161).

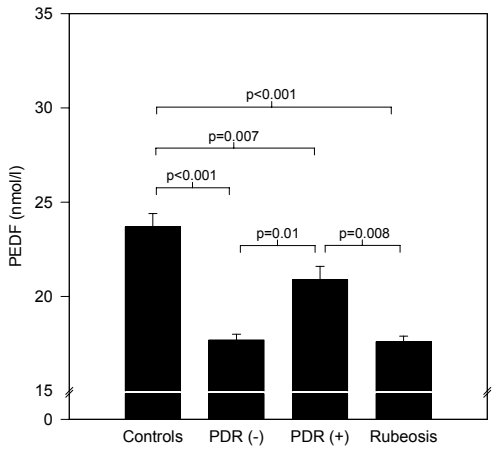

Figure 21: Levels of vitreal PEDF depend upon previous photocoagulation. PDR (-) are patients with PDR without prior photocoagulation; PDR(+) are patients with PDR with prior photocoagulation.
Rubeosis are non-diabetic patients with extensive retinal neovascularization due to central vein occlusion.

Presumably, a reduction in retinal ischemia after photocoagulation increases expression of physiologically expressed and hypoxia-dependent downregulated angiogenesis inhibitors such as PEDF. Indeed, PEDF expression was initially induced by hyperoxia in neonatal mice (127).

In addition to the hypoxia dependent regulation of PEDF, local release of angiogenesis-inhibitors might occur as a consequence of "wound healing" within the retina. Angiostatin, a fragment encompassing the kringle region of plasminogen, has been identified and characterized as a potent inhibitor of neovascularization (162). We were able to demonstrate an association between release of the angiogenesis inhibitor angiostatin with previous retinal scatter photocoagulation (111). Regulation of these changes seems to occur locally, since angiostatin was not measurable in relevant amounts in human serum, while the angiostatin precursor plasminogen could be demonstrated within all samples investigated. The regulation of angiostatin

release remains unclear. This study provided data that plasminogen occurs in considerable amounts in the vitreous of control and diabetes patients.

A

Subjects	N	Age (y)	Female	Male	Duration of Diabetes (y)	HbA1c (%)	Angiostatin neg	Angiostatin pos
Controls	18	68.7±3.7	10	8	_	5.1±0.1	16	2
Proliferative Diabetic Retinopathy	34	61.1±3.2	17	17	17.6±1.9	8.0±0.3	9	25
- with photocoagulation	26	63.2±6.8	13	13	18.8±2	8.1±0.2	2	24
- without photocoagulation	8	60.6±2.5	4	4	15.5±4.5	7.7±0.7	7	1

B

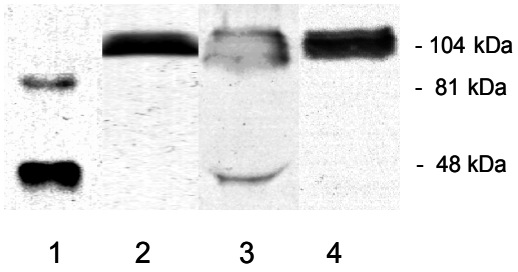

Figure 22: (A) Frequency of intraocular angiostatin detection in patients with proliferative diabetic retinopathy with and without prior photocoagulation and in control individuals. (B) Western blots with a polyclonal plasminogen antibody. Control lanes with angiostatin (Lane 1) and with human plasminogen (Lane 2). Both, angiostatin and plasminogen could be detected in human vitreous (Lane 3). The band sized 43 kDa did not appear after preincubation of the antibody with angiostatin K1-4 fragment thereby demonstrating specificity of reaction (Lane 4).

Recently a macrophage-derived metalloproteinase has been shown to generate angiostatin in Lewis Lung carcinoma (163). It is tempting to speculate that a similar process with activation of macrophages, expression of macrophage-derived metalloelastase and production of angiostatin from pre-existing plasminogen occurs in the retina after retinal photocoagulation. Whether angiostatin is generated only after scatter photocoagulation or whether a similar mechanism appears after focal

photocoagulation and might explain at least in part its positive therapeutic effects is unclear.

However, it remained unclear why the investigated patients had a progression of retinopathy requiring retinal surgery despite scatter photocoagulation and the above mentioned reduction of VEGF, elevation of PEDF and release of angiostatin . In this respect it is noteworthy that the intraocular VEGF levels were still about 10-fold elevated compared to control individuals despite previous photocoagulation (111) and PEDF-concentrations of patients after retinal scatter photocoagulation remained below those of control patients. Obviously a "cocktail" of various cytokines finally triggers angiogenesis or its inhibition. Recent studies showed the potential necessity of the IGF-system for angiogenesis in vivo (132). Interaction between IGF-I and the IGF-I receptor does not directly influence the expression of VEGF/VPF or its receptors (IF-IR). However, antagonism of the IGF-IR suppresses VEGF/VPF-stimulated activation of the mitogen-activated protein kinase (MAPK) pathway in retinal endothelial cells. IGF-I possibly regulates the synthesis of one or more of the components of the VEGF dependent MAPK pathway and might thereby mediate the permissive effects of IGF-I on VEGF/VPF induced retinal angiogenesis (132). In ocular fluid unchanged levels of IGF-I and IGF-II after retinal scatter photocoagulation were demonstrated and might offer a mechanism, by which substantially reduced levels of VEGF/VPF might still promote retinal angiogenesis after retinal photocoagulation (146).

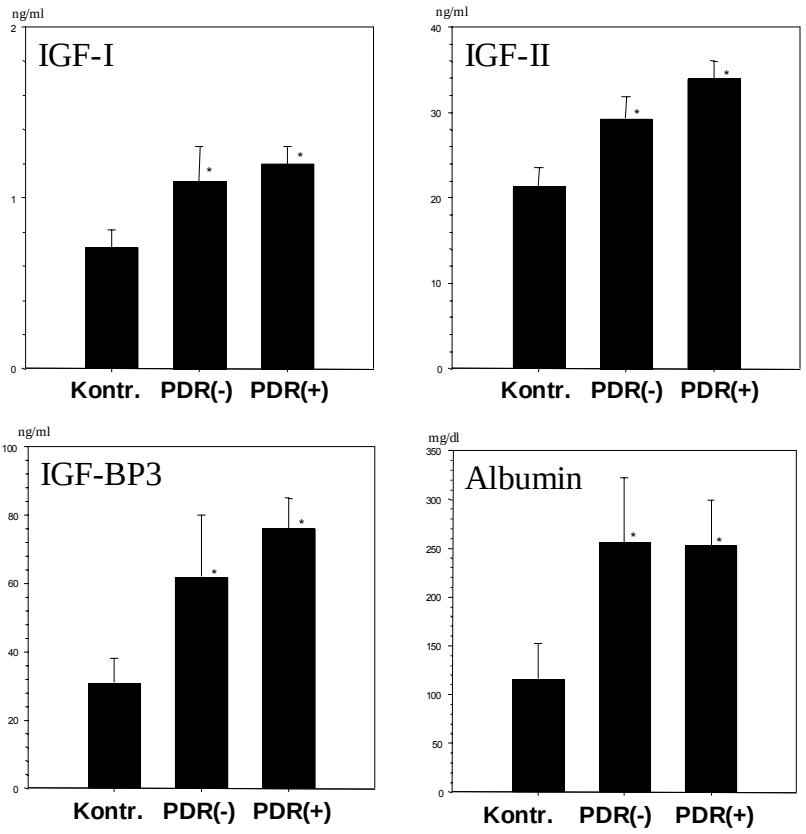

Figure 23: Levels of intraocular IGF-I, IGF-II, IGF-BP3 and albumin are elevated in patients with proliferative diabetic retinopathy with (PDR(+)) and without (PDR(-)) previous photocoagulation compared to controls.

It is, however, possible that patients treated effectively by lasercoagulation might have an improved function of the blood retina barrier and reduced levels of IGF-I, IGF-II and IGF-BP3 intraocularly. These patients are not amenable to investigation and therefore, other techniques will have to be employed to answer this question. These findings have direct clinical relevance, since the elevated levels of IGF´s rationalize an unsuccessful lasercoagulation in patients with proliferative diabetic retinopathy. Thus, our findings indicate that a combined treatment with somatostatin analogues to control intraocular IGF-I levels and retinal scatter photocoagulation surgery might be a useful approach in patients with proliferative diabetic retinopathy and failure of retinal photocoagulation.

In summary, we have shown that retinal photocoagulation has considerable impact on intraocular concentrations of angiogenic and anti-angiogenic cytokines (110, 111, 146). While VEGF can be reduced, the angiogenesis inhibitors like PEDF are replenished and angiostatin is even newly released into the vitreous. In contrast, photocoagulation appeared to have no direct effect on local IGF-levels, which might explain, why the investigated patients still had progression of their retinopathy finally requiring vitreal surgery.

3.4 Therapeutic implications

Despite strong metabolic control and appropriate ophthalmologic treatment some patients apparently still show a progression of vascular diabetic complications. These patients foster the search for additional therapeutic options, which obviously might be based on the existing knowledge on the pathogenesis of diabetic retinopathy. However, as positive the explosion of knowledge on the pathogenesis of diabetic complications is, so questionable is the implementation of these findings in terms of clinical outcome. With the exception of triamcinolone treatment in diabetic macular oedema, no experimental approach has yet reached clinical significance, although some of them have been tested already in clinical phase III trials. Various experimental therapeutic approaches have been implemented, as partially shown in Table 10. Future needs to show, whether some of them proof to be useful and will finally reach clinical practise.

Standard treatment	• metabolic control • retinal photocoagulation • vitrectomy
Experimental strategies **Systemic therapies**	
Inhibition of aldose reductase	• sorbinil • tolrestat • epalrestat • fidarestat
Inhibitors of protein glycation	• aminoguanidine • pyridoxamine
Antioxidants	• vitamin A • vitamin C • vitamin E
Inhibitors of PKC	• LY333531 • LY379196 • PKC412
Inhibition of GH/IGF-I axis	Somatostatin analogues: • octreotide • somatuline GH receptor antagonist: • pegvisomant
Local therapies	
Inhibition of VEGF	• rhuFab VEGF • EYE001
Steroid compounds	• triamcinolone acetonide • fluocinolone acetonide • anecortave acetate
Gene therapy	Recombinant virus vectors delivering transgenes encoding angiostatic molecules • VEGF antagonists • PEDF
Stem cell therapy	Delivery of endothelial precursors transfected with angiostatic molecules • T2-TrpRS

Table 10: Standard and experimental therapeutic options in diabetic retinopathy

Taken together, intensive metabolic control is still the most important goal of treatment, as it is known to prevent microvascular complications in patients with type 1 and type 2 diabetes mellitus (164-166). Additional tight blood pressure control further prevents development of microvascular complications (167). Thus, the existing data clearly show that the implementation of strong metabolic and blood pressure control as early as possible and the maintenance of therapy for as long as possible is of utmost importance. Even the benefits of an intermediate improvement of blood glucose control persist over long time periods, suggesting a vascular memory for metabolic events (165).

Retinal photocoagulation is a well established therapy in patients with advanced diabetic retinopathy. The Diabetic Retinopathy Study found that treatment with photocoagulation is able to reduce severe visual loss by about 50% (168). Results of the Early Treatment Diabetic Retinopathy Study showed a favourable effect of photocoagulation in patients with severe NPDR and therefore use of scatter photocoagulation and before onset of proliferative retinopathy has been suggested (160).

Currently ,and before any other treatment strategy, it remains mandatory to apply standard therapy to the patients with improving metabolic control, strong regulation of blood pressure and specific ophthalmologic treatment if required.