4. Summary

Hyperalimentation and sedentary lifestyle contribute to the increase of nutritive diseases worldwide, including type 2 diabetes mellitus. Cytokines are known to play a role in the pathogenesis of type 2 diabetes mellitus and given the pleiotropic nature of these factors, it is not surprising, that the development of vascular diabetic complications is also influenced by such proteins.

The work of the applicant focused on two topics, the role of cytokines in the development of type 2 diabetes mellitus and their regulation in the pathogenesis of proliferative diabetic retinopathy, a major microvascular complication of diabetes mellitus.

With respect to type 2 diabetes, inflammatory cytokines and adiponectin were analysed in two independent cohorts. Women with the polycystic ovary syndrome (PCOS) were investigated, as these patients display a high risk phenotype for future type 2 diabetes and are frequently insulin resistant. Interleukin-6, a central inflammatory cytokine, was basically associated with anthropometric changes, rather than PCOS itself (21). Since adiponectin is related to insulin sensitivity its contribution to this phenotype was also analysed in women with PCOS. Indeed adiponectin contributed considerable to the variation of insulin sensitivity, while BMI, age and testosterone levels were the remaining contributors (22). In a second prospective cohort, interleukin-6 and interleukin-1ß were elevated prior to onset of type 2 diabetes and were found to interact in the prediction of the disease (6). Thus only individuals with elevated levels of IL-6 and detectable levels of IL-1ß had an increased diabetes risk, supporting the hypothesis that these inflammatory cytokines operate as networks and participate in the pathogenesis of type 2 diabetes. In addition, a polymorphism within the IL-6 promoter was subsequently described, that

modified the BMI-dependent diabetes risk (23). Although obesity is well established as a risk factor for type 2 diabetes, a relatively high proportion of individuals does never experience the disease despite being obese. High levels of adiponectin were associated with a substantially reduced incidence of type 2 diabetes, suggesting that this protein might indeed effectively protect against the disease (95). Additionally the down-regulation of adiponectin by insulin was demonstrated in vivo in man, which supported the hypothesis that insulin resistance and the subsequent hyperinsulinemia might itself contribute to hypoadiponectinemia and thereby promote development of type 2 diabetes (99).

The second focus of the applicant was the role of cytokines in the pathogenesis of proliferative diabetic retinopathy. The eye provides an ideal setting to investigate angiogenesis in vivo in man, as retinal proliferation can be directly quantified and intraocular levels of potential angiogenic or anti-angiogenic cytokines can be determined within the vitreous of patients who undergo vitreal surgery. The regulation of cytokines can finally be correlated to the degree of retinal angiogenesis. The applicant has demonstrated that proliferative diabetic retinopathy is associated with an up-regulation of angiogenic cytokines like VEGF, bFGF and IGFs (111, 145). The major source of intraocular IGFs appears to be the circulation, which suggests that systemic IGF-lowering treatment with i.e. somatostatin-analogues may be a helpful therapeutic approach in specific clinical situations (145). In addition, a down-regulation of the anti-angiogenic cytokine PEDF was demonstrated, suggesting that PEDF might be an important physiological angiogenesis-inhibitor within the eye (110). Finally the regulation of cytokines was investigated with respect to the role of retinal photocoagulation, which is a standard therapy in patients with proliferative diabetic retinopathy. Indeed, the release of the angiogenesis inhibitors angiostatin, replenishment of PEDF and a reduction of angiogenic factors like VEGF was found

(110, 111). However, in contrast to VEGF, IGFs were not reduced in patients after retinal photocoagulation (146).

In summary, the applicant has demonstrated a role of various adipocytokines in the development of type 2 diabetes mellitus. A complex interplay of intraocular pro- and anti-angiogenic cytokines has been shown in proliferative diabetic retinopathy.