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Factors predicting progression of chronic kidney disease in IgA Nephropathy

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ABSTRACT

Glomerulonephritis (GN) is the main cause of chronic kidney disease (CKD) in patients on renal replacement therapy, with IgA nephropathy (IgAN) being the most frequent single diagnosis. Patients with reduced kidney function and/or proteinuria have an increased risk of premature cardiovascular disease (CVD). Based on the assumption that progression of atherosclerosis and glomerulosclerosis share similar pathogenetic mechanisms, the aim of this thesis was to investigate to which extent some of the described traditional and non-traditional cardiovascular risk factors are also predictors of renal outcome in patients with a homogenous renal diagnosis, e.g. IgAN. Chronic inflammation is supposed to be one of the driving forces in renal disease progression, and disturbances in both innate and adaptive immunity seem to be involved in the pathogenesis of IgAN, with T-lymphocytes being of particular interest. We therefore also investigated the prognostic impact of plasma levels of soluble interleukin-2 receptor, suggested as a marker of continuous T-cell stimulation.

Study I was a pilot study, investigating activated monocytes (MOs) as one possible source of oxidative stress in IgAN. Peripheral blood MOs from 16 patients with IgAN and 16 healthy controls were stimulated *in vitro* and the production of reactive oxygen species (= respiratory burst) was measured by flow cytometry. In the patients, this was repeated after one month's treatment with 20 mg atorvastatin. At baseline, the respiratory burst of *in vitro* stimulated MOs was higher in patients as compared to in healthy controls. After atorvastatin treatment, there was a significant reduction of unstimulated and stimulated MO respiratory burst compared to baseline values.

In **study II**, the apolipoprotein B /apolipoprotein A-I ratio (apoB/apoA-I), indicating the balance of atherogenic and anti-atherogenic lipids, was analyzed in 70 IgAN patients with CKD stage 1-3 (estimated glomerular filtration rate (eGFR) ≥ 30ml/min/1.73m²) and in 70 age- and gender matched healthy control subjects. Patients with IgAN had higher serum levels of apoB/apoA-I compared to the controls, and an apoB/apoA-I ratio greater than the proposed threshold value of 0.9 for men and 0.8 for women was associated with an increased risk for the development of end stage renal disease (ESRD) in the patients, after a median follow-up period of 3.8 years.

Study III comprised 194 patients with IgAN, of whom 179 with CKD stage 1-4 (eGFR ≥15ml/min/ 1.73m²) had been prospectively followed for up to 16 years (median 52 months). Plasma levels of soluble interleukin-2 receptor alfa unit (sIL-2Ra) were higher in IgAN patients compared to in 84 healthy controls. In survival analysis, baseline sIL-2Ra levels in the upper tertile predicted worse renal outcome in IgAN patients. Soluble IL-2Ra also correlated to the rate of renal function decline (annual eGFR slope). In 51 patients, in whom the renal biopsy had been scored according to the new Oxford classification, higher IL-2Ra levels were associated with the presence of more than 25% tubular atrophy/ interstitial fibrosis (T score 1-2), after adjustment for renal function.

Study IV was performed in 180 IgAN patients with CKD stage 1-4, followed for a median of 55 months. Baseline serum levels of fibroblast growth factor 23 (FGF23), a key player in the chronic kidney disease-mineral and bone disorder (CKD-MBD), were associated with severe renal outcome and with the annual eGFR slope. Moreover, the FGF23 level at baseline correlated to the degree of albuminuria at baseline and to time-averaged albuminuria during follow-up, a new finding that implicates possible direct effects of FGF23 on the glomerular filtration barrier.

In **Summary**, several factors involved in the progression of atherosclerosis are also present and predictive of renal outcome in patients with IgAN, independent of the confirmed main risk factors: proteinuria and hypertension. Furthermore, continuous T-cell stimulation may contribute to renal disease progression in IgAN. The investigated potential biomarkers could be useful in the monitoring of the therapy.

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