Angiopoietin 2 and Cardiovascular Disease in Dialysis and Kidney Transplantation

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Background: Accelerated atherosclerosis in patients with chronic kidney disease (CKD) is still incompletely understood. Angiopoietin 1 (Ang-1) and Ang-2 are 55-kDa antagonistic nonredundant gatekeepers of endothelial activation and thus are potential important factors in accelerated atherosclerosis. We aimed to study: (1) angiopoietin levels in patients treated by means of dialysis and kidney transplantation, (2) the association of altered angiopoietin levels with atherosclerosis, and (3) changes in altered levels after renal transplantation.

Study Design: Cross-sectional and longitudinal observational study.

Setting & Participants: 117 patients with CKD (61 hemodialysis [HD] patients, 24 peritoneal dialysis [PD] patients, and 32 renal transplant recipients) and 22 healthy controls.

Predictor: Treatment by means of HD or PD or renal transplantation versus healthy controls.

Outcome: Serum Ang-1 and Ang-2 levels and ratio and changes in levels before and 3 months after transplantation. Correlations of angiopoietin levels with the presence and severity of coronary heart disease and peripheral arterial disease.

Measurements: Ang-1 and Ang-2 were measured in sera by using an immunoradiometric sandwich assay and enzyme-linked immunosorbent assay, respectively. Coronary heart disease was scored by using coronary angiography, and peripheral arterial disease, by using ultrasonography.

Results: Ang-1 level was decreased in HD patients compared with controls (29.1 $\pm$ 12 versus 45.3 $\pm$ 11.5 ng/mL; $P < 0.001$). In contrast, Ang-2 level was increased (HD, 8.7 $\pm$ 0.64; PD, 6.48 $\pm$ 8.1 ng/mL versus controls, 0.88 $\pm$ 0.43 ng/mL; $P < 0.001$). Ang levels in renal transplant recipients were not different from healthy controls. Longitudinally, individual Ang-2 levels decreased after kidney transplantation ($P = 0.01$). In addition, in patients with CKD, Ang-2 level correlated significantly with scores of coronary heart disease ($r = 0.486$; $P < 0.001$) and peripheral arterial disease ($r = 0.648$; $P < 0.001$).

Limitations: Cross-sectional study design.

Conclusions: Circulating Ang-2 level was increased in patients treated with dialysis, although the mechanism is unknown. Kidney transplantation normalized circulating Ang-2 levels after 3 months. In addition, Ang-2 might be a mediator (and thus a marker) that accounts for accelerated atherosclerosis in dialysis patients.

Am J Kidney Dis 53:770-778. © *2009 by the National Kidney Foundation, Inc.*

INDEX WORDS: Angiopoietin; Ang-1; Ang-2; atherosclerosis; cardiovascular disease (CVD); coronary heart disease (CHD); peripheral arterial disease (PAD); hemodialysis; dialysis; renal transplantation; kidney.

About 13% of the US population has some degree of chronic kidney disease (CKD).[1] These patients are more likely to die of cardiovascular disease than develop overt kidney failure.[2] However, the pathogenesis of atherosclerosis in patients with CKD is different from that in the general population, epitomized best by studies in end-stage renal disease. There, classic cardiovascular risk factors sometimes not only fail to predict survival and cardiovascular burden, but show a reverse epidemiology.[3] Some new cardiovascular risk factors are more powerful, indicating cardiovascular disease[4,5] or endothelial function[6] or predicting mortality[7] in patients with end-stage renal disease. These new markers also help us understand the complex pathophysiological state of cardiovascular disease in patients with CKD.[8]

Recently, angiopoietins (molecular weight, ~55 kDa), growth factors involved in angiogenesis and vasculogenesis,[9] have been identified. Angiopoietin 1 (Ang-1) and Ang-2 are ligands of

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Received July 22, 2008. Accepted in revised form November 13, 2008. Originally published online as doi: 10.1053/j.ajkd.2008.11.030 on March 6, 2009.

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0272-6386/09/5305-0009$36.00/0
doi:10.1053/j.ajkd.2008.11.030

the Tie-2 receptor, a second class of vascular-specific receptor tyrosine kinases. The angiopoietin/Tie system tightly controls the endothelial phenotype during angiogenesis in a unique and nonredundant fashion.[10,11] Ang-1 preserves vessel integrity by activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway.[12] Additionally, vascular endothelial growth factor (VEGF) regulates Ang/Tie-2 signaling by inducing proteolytic cleavage and shedding of Tie-2 through a PI3K/Akt-dependent pathway; therefore, VEGF may inhibit vascular stabilization in an angiopoietin-dependent manner.[13] Ang-1 protects the adult vasculature against plasma leakage[14]; thus, experimental overexpression of Ang-1 during sepsis reduces mortality because of preserved vessel integrity.[15]

In a dose-dependent manner, Ang-2 competitively inhibits binding of Ang-1 to Tie-2, followed by loss of vessel integrity, vascular leakage, and induction of inflammatory gene expression.[11] Accordingly, angiopoietin disequilibrium has been found in patients with diabetes mellitus,[16] cardiac allograft arteriosclerosis,[17] acute coronary syndrome,[18] and sepsis.[19] Moreover, glomerular Ang-2 is upregulated in preclinical models of glomerulonephritis,[20] and podocyte-specific expression of Ang-2 causes proteinuria.[21] Recently, the balance between Ang-1 and Ang-2 has been found in favor of Ang-2 in atherosclerotic plaques with high microvessel density.[22]

Although abnormal serum angiopoietin levels have been reported in various cohorts with concomitant vascular disease,[16,18] patients with CKD have not been investigated to date. Regarding these patients' high risk of the accelerated development of atherosclerosis and the still unsolved question of the underlying mechanism(s), we aimed to: (1) investigate angiopoietin homeostasis in patients with CKD, (2) detect the impact of disturbed angiopoietin balance as a potential mediator for atherosclerosis, and (3) survey the role of kidney function by measuring individual circulating angiopoietins before and after renal transplantation.

METHODS

The study was approved by the local Ethics Committee of Hannover Medical School, Hannover, Germany (No. 4373). All patients gave written informed consent. We studied 117 stable white patients with CKD. Twenty-two healthy volunteers (12 men, 10 women) served as controls. Patients with stage 5 CKD were treated with different modes of dialysis and kidney transplantation. Sixty-one patients (37 men, 24 women) were on hemodialysis (HD) therapy for at least 12 weeks before the study, and 24 (12 men, 12 women) were treated with peritoneal dialysis (PD). In addition, we studied 32 renal transplant recipients (RTRs; 20 men, 12 women) at follow-up visits (3 months after transplantation) from the Hannover protocol biopsy program.[23] Angiopoietin levels of

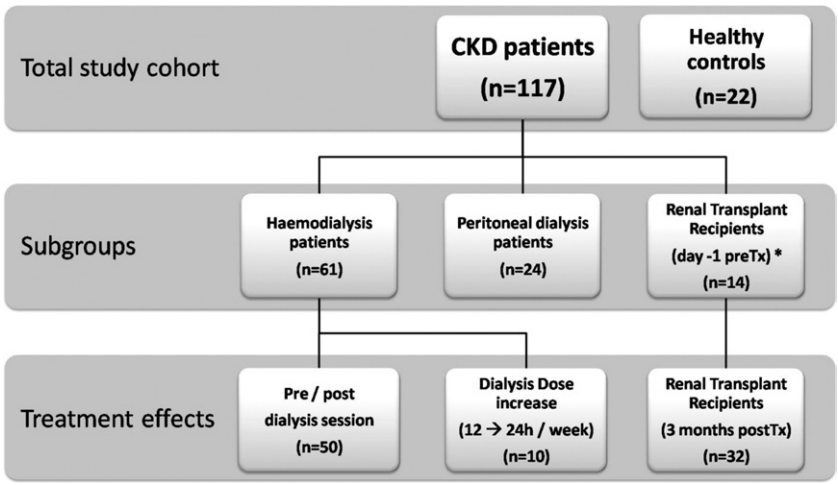

Figure 1. Flow chart shows the different study groups (level 2) and subgroups (level 3) for all patients with chronic kidney disease (CKD; level 1) and such treatment effects as dialysis-associated angiopoietin alterations (level 3, left side) and effects of renal transplantation (Tx; level 3, right side). *Thirty-two renal transplant recipients (RTRs) were evaluated cross sectionally (angiopoietin level and vascular bed–specific atherosclerosis). To longitudinally assess angiopoietin level courses, angiopoietin 2 has been measured retrospectively using stored samples from 1 day before renal transplantation in 14 of those RTRs.

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