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EXPRESSION OF ANGIOPOETIN ON THE KIDNEY TRANSPLANT WAITING LIST: A SINGLE-CENTER STUDY

BÖBREK NAKLİ BEKLEME LİSTESİNDEKİ HASTALARDA ANJİYOPOETİN'İN İFADESİ: TEK MERKEZLİ BİR ÇALIŞMA

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ABSTRACT

Objective: Angiopoietin-2 (Ang-2) is a growth factor belonging to the angiopoietin (Ang)/Tie signaling pathway. Plasma levels of especially Ang-2, are thought to be significantly increased in patients with acute kidney injury (AKI), independent of inflammation. Ang-2 is also important in dialysis and transplantation, as it plays an important role in the disruption of endothelial homeostasis. Our study aimed to investigate the relationship between anti-HLA antibody loads and Ang levels in patients with end-stage renal disease (ESRD) who are on the organ transplant waiting list.

Material and Method: 80 ESRD patients who were on the waiting list between 2018 and 2020 and whose panel reactive antibody (PRA) screening and identification test were studied participated in our study. First, the PRA screening test was performed on the patients, and the class I-II identification tests were studied on the patients who were positive for PRA. The Ang-2 level was evaluated by the ELISA method. The relationship between Ang-2 levels and PRA percentages in PRA positive and negative patients was evaluated.

Results: A positive correlation was found between anti-HLA antibody and Ang-2 levels in patients with ESRD (class I, p=0.024; class II, p=0.032), and a statistically significant increase in Ang-2 level was found in patients with PRA ≥50% positive (class I, p=0.038) This finding suggests that Ang-2 may have an important role in the progression of chronic renal failure and may be effective in predicting graft survival after transplantation.

Conclusions: Further studies will be required to fully elucidate the effect of Ang-2 on renal progression.

Keyword: Angiopoetin-2, anti-HLA antibody, kidney transplantation

ÖZ

Amaç: Anjiyopoietin-2 (Ang-2), anjiyopoietin (Ang)/Tie sinyal yolağına ait bir büyüme faktörüdür. Akut böbrek hasarı (AKH) olan hastalarda inflamasyondan bağımsız olarak özellikle Ang-2'nin plazma düzeylerinin önemli ölçüde arttığı düşünülmektedir. Ang-2, endotel homeostazının bozulmasında önemli bir rol oynadığı için diyaliz ve transplantasyonda da önemlidir. Çalışmamızda organ nakli bekleme listesinde olan son dönem böbrek hastalığı (SDBY) hastalarında anti-HLA antikor yükleri ile Ang düzeyleri arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmamıza 2018-2020 yılları arasında panel reaktif antikor (PRA) tarama ve tanımlama testi çalışılmış bekleme listesinde bulunan 80 SDBY (son dönem böbrek yetmezliği) hastası katıldı. Hastalara önce PRA tarama testi, PRA pozitif çıkan hastalara sınıf I-II tanımlama testleri çalışıldı. Ang-2 düzeyi ELISA yöntemi ile değerlendirildi. PRA pozitif ve negatif hastalarda Ang-2 düzeyleri ile PRA yüzdeleri arasındaki ilişki değerlendirildi.

Bulgular: SDBY olan hastalarda anti-HLA antikoru ile Ang-2 düzeyleri arasında pozitif korelasyon (sınıf I, p=0,024; sınıf II, p=0,032) ve PRA ≥%50 pozitif olan hastalarda Ang-2 düzeyinde istatistiksel olarak anlamlı bir artış bulundu (sınıf I, p=0,038). Bu bulgu, Ang-2'nin kronik böbrek yetmezliğinin ilerlemesinde önemli bir rolü olabileceğini ve nakil sonrası greft sağkalımını tahmin etmede etkili olabileceğini düşündürmektedir.

Sonuç: Ang-2'nin renal progresyon üzerindeki etkisini tam olarak aydınlatmak için daha ileri çalışmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Anjiyopoetin-2, anti-HLA antikoru, böbrek nakli

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INTRODUCTION

Angiopoietins (Angs) are an important vascular growth factor family which is composed of the members Ang-1, Ang-2, Ang-3, and Ang-4 and is involved in multiple cellular functions related to cell survival, cell growth, and cell migration. The best-characterized members of this family are Ang-1 and Ang-2, and their activities are mediated by tyrosine kinase receptors (Tie-1 and Tie-2). Ang-1 is a strong angiogenesis growth factor, which transmits signals by way of Tie-2, while Ang-2 is a growth factor belonging to the angiopoietin (Ang)/Tie signaling pathway, which is one of the main pathways involved in angiogenesis. It has been reported that Ang-2 binds to the Tie-2 receptor with a similar binding affinity and induces its inhibitory role, while it does not bind to Tie-1 (1-3).

The Ang/Tie-2 signaling axis is an important modulator of vascular integrity, and Tie-2 receptors are extensively expressed in endothelial cells (4). Activation of Tie-2 signaling strengthens interendothelial junctions and reduces the expression of leukocyte adhesion molecules (5). Studies have reported that Ang-2 can antagonize the stability action of Ang-1 by competitively binding to Tie-2 in pathological conditions, and thus, it can lead to vascular instability, reduce cell-to-cell adhesion, and activate beta-1 integrin to encourage endothelial inflammation by disrupting the protective Ang-1/Tie-2 signaling pathway (6,7). The Ang-2 expression may be triggered by inflammatory mediators (8,9). Studies which used targeted manipulations of Ang/Tie-2 signaling by way of tools such as genetic approaches, antibodies, and RNA intervention showed that end-organ injury and hemodynamic changes occurring in experimental sepsis and hepatic disease were associated with an excessive increase in Ang-2 (10).

Angs, belonging to the vascular growth factor family, is widely expressed in the kidneys and is thought to maintain the structure of the glomerular filtration barrier. Studies in the literature have reported that Ang-Tie signaling is important for the efficient functioning of the renal microvascular system. In a study conducted with patients, who had lupus nephritis, it was reported that Ang-2 protein expression was prominent in glomerular endothelium, and serum Ang-2 levels were closely associated with the severity of systemic lupus erythematosus (SLE) (11). In addition, the same researchers showed that serum Ang-2 levels were significantly higher in patients with ANCA-related vasculitis and renal involvement compared to healthy individuals (11). The results of these studies suggest that inflammatory damage to the kidneys may result in the release of Ang-2 from the renal endothelium. Acute kidney injury (AKI) is closely associated with sepsis (12). Ang-2 level increases in response to sepsis, and as a result, the endothelial barrier structure is disrupted, and microvascular permeability increases (13). Studies have reported that plasma levels of especially Ang-2, among endothelial biomarkers, significantly increase independent of inflammation in critical patients with AKI, and Ang-2 is associated with the development of late-onset AKI (14).

Ang-2 is also important in dialysis and transplantation, as it is effective in disrupting endothelial homeostasis. Studies show that circulating Ang-2 levels increase in patients receiving dialysis treatment, and these results suggest that Ang-2 can be used as a marker to detect cardiovascular disorders that occur during dialysis, especially in childhood (15,16).

During organ transplantation, ischemia-reperfusion (I/R) injury may occur to a great extent. It is thought that endothelial irregularity is an important pathogenic outcome of I/R injury, and this complication plays an important role in patient/graft survival (17).

In a study using the renal I/R model, it was reported that the imbalance in the Ang-1/Ang-2 ratio caused an increase in pericyte proliferation, endothelial cell loss, and fibrosis (18). In studies conducted with patients with I/R injuries and undergoing dialysis, it has been reported that the increase in Ang-2 promotes plasma and leukocyte leakage by causing a loss in the endothelial glycocalyx (eGC) (19).

Fibrosis is a complication that may result in disease progression and graft loss after kidney transplantation. It occurs especially in the first three months after transplantation is triggered by inflammation following reperfusion injury and continues with a sustained inflammatory immune response that supports the progression of kidney disease (20). The presence of anti-human leukocyte antigen (HLA) antibodies in the recipient increases the risk of antibody-mediated rejection (AMR) after kidney transplantation (21). Subclinical AMR, which may occur with the presence of donor-specific antibodies, is a strong profibrotic stimulus and may provide a prediction of graft loss (20). Therapeutic strategies used to minimize the risk of progression of fibrosis in renal grafts have reduced the incidence of clinical rejection developing in the first few years following transplantation, and early fibrosis markers have become important markers for renal function and graft survival.

In our study, we aimed to investigate the relationship between anti-HLA antibody loads and Ang levels in patients included on organ transplant waiting lists because of end-stage renal disease (ESRD).

MATERIAL and METHOD

Eighty patients with ESRD, who were included on the renal transplant waiting list between 2018 and 2020 and underwent panel reactive antibody (PRA) screening and identification test, were included in our study. PRA screening test was primarily performed in all patients using life codes kits (immucor Medizinische Diagnostik GmbH Robert-Bosch-Strasse, Dreicich Germany). In 40 patients whose screening tests were found to be positive, class I and class II identification tests were performed again using lifecodes kits (immucor Medizinische Diagnostik GmbH Robert-Bosch-Strasse, Dreicich Germany) with the Luminex method in accordance with the manufacturer's instructions. In PRA screening and identification tests, a mean fluorescence intensity (MFI) value of >1000 was considered positive.

Table 1: Ang-2 levels in PRA positive and negative patients

		PRA positive	PRA negative		p
Ang-2		888.54±287.58	866.57±239.93		0.548
			PRA positive patients		
	Group	**Class I positive**	**p**	**Class II positive**	**p**
Ang-2	**1. group ≤30**	785.29±289.63	1 vs 2 p=0.898 1 vs 3 p=0.089 2 vs 3 **p=0.046***	754.39±300.51	1 vs 2 p=0.994 1 vs 3 p=0.483 2 vs 3 p=0.976
	2. group 31-60	711.87±242.68		840.46±257.75	
	3. group 61-100	969.20±341.76		932.82±291.31	
	Group	**Class I positive**	**p**	**Class II positive**	**p**
Ang-2	**≤50**	750.25±346.45	**0.038***	804.68±251.44	0.197
	≥50	944.50±258.33		923.07±302.53	

Ang-2: Angiopoetin-2, PRA: Panel reactive antibody

In addition, the Ang-2 level was studied and evaluated using the ELISA (Enzyme-Linked ImmunoSorbent Assay) method (Invitrogen-ThermoFisher Scientific-catalogue number: KHC1641) in accordance with the manufacturer's instructions (Range; 2.236-621 pg/mL) in the sera in which PRA identification tests were studied. The PRA-positive patients included in our study were primarily divided into 3 groups (Group 1=≤30%; Group 2=31%-60%; Group 3= 61%-100%) and later divided into two groups (Group 1=0%-50%; Group 2=50%-100%) according to PRA positivity percentage values. The relationships between Ang-2 levels and PRA percentages in each group were evaluated as well.

This study was approved by Demiroglu Bilim University Clinical Research Ethics Committee (Date: 02.08.2022, No: 2022-15-02).

RESULTS

Among the 80 patients with ESRD who were included in the study, 57.5% (n:46) were female, and 42.5% (n:34) were male. The mean age was 49.54±19.43 years in the whole patient group, 39.50±21.09 years in the female patients, and 35.80±33.20 years in the male patients.

The PRA screening and identification tests were found to be positive in 50% of the patients (n:40) (MFI>1000) and negative in the other 50% (n:40) (MFI<1000). Class I PRA was found to be positive in all 40 patients (100%) who had a positive PRA result. Class II PRA was found to be positive in 39 (97.5%) patients and negative in 1 patient (2.5%). There was no statistically significant difference in Ang-2 levels between PRA-positive patients and PRA-negative patients (p=0.548). The PRA-positive patients included in our study were divided into 3 groups according to PRA positivity percentage values (Group 1=≤30%; Group 2=31%-60%; Group 3=61%-100%), and the relationship between Ang-2 levels and PRA percentages was evaluated in each group. Oneway Anova post hoc test (Bonferroni) was used for the evaluation of Class I and Class II PRA positivity percentages, and when the relationship between PRA positivity percentages and Ang-2 levels was examined, it was found to be significant with class I, but no significant relation was found with class II (respectively class I; p=0.049, class II; p=0.335) (Table 1). Considering the Ang-2 levels between the 3 groups in Class I PRA, a significant difference was found between the 2nd group and the 3rd group (p=0.046).

When the PRA-positive patients were divided into two groups according to positivity percentage (Group 1=0%-50%; 2. Group 2=50%-100%) and the relationships between PRA positivity percentages and Ang-2 levels were compared using the Independent Sample t-test, it was found that Ang-2 levels were significantly higher in the patients whose class I PRA percentages were higher than 50% (p=0.038). A difference reaching statistical significance could not be found between the two groups for the relationship between class II PRA percentages and Ang-2 levels (p=0.197) (Table 1).

When the correlation between Ang-2 levels and class I and class II PRA positivity percentages was evaluated in the PRA positive group, a significant positive correlation (Pearson correlation) was found between Ang-2 and class I positivity (r=0.362, p=0.024) and class II positivity (p=0.348, p=0.032) (Table 2).

Table 2: Correlation between Ang-2 levels and Class I and Class II PRA positivity percentages

PRA positive patients	Ang-2	Class I	Class II
Pearson Correlation (r)	1	0.362	0.348
p		0.024	0.032
N		40	39

Ang-2: Angiopoetin-2, PRA: Panel reactive antibody

DISCUSSION

Angs are vascular growth factors whose functions are mediated by Tie tyrosine kinase receptors. Competitive binding of Ang-2 to the Tie-2 receptor disrupts the vasculature and basal lamina (22). Although it is known that Ang-2 is mostly synthesized by endothelial cells, which have important effects on vascular development, it can also be synthesized and released by other cell types. The release of Ang-2 leads to inflammation. Therefore, it has been associated with many pathological conditions (23).

It is thought that Ang-2 levels are associated with systemic inflammation markers/mediators in patients with chronic renal failure (CRF). In addition, it has been reported in various studies that Ang-2 levels increase in dialysis patients due to the progression of chronic kidney disease (CKD) (17,18). In studies with preclinical glomerulonephritis models, it has been reported that glomerular Ang-2 is up-regulated, and this causes proteinuria (24). It is known that the CVD incidence is higher in patients with ESRD who receive hemodialysis. In studies conducted with ESRD patients undergoing hemodialysis, it has been reported that endothelial dysfunction is associated with an increased incidence of CVD (17,18). One study reported a strong and consistent association between serum Ang-2 levels and mortality, even when most risk factors were excluded (25).

Anti-HLA donor-specific antibodies are the most important factor leading to AMR. The PRA test generally predicts the percentage of potential donors who possess a recipient's HLA antibodies and approximately displays the risk of positive crossmatching. When compared with solid phase tests, it is more sensitive for antibodies with lower titers and allows more precise specification of specific HLA antigens and alleles (26). In association with negative kidney graft results, a few non-HLA antibodies have been identified (endothelial antibodies, epithelial antibodies, or antibodies to various proteins). Most data related to non-HLA antibodies in liver transplantation originate from observational studies in which antibodies to antigens were identified (Table 1) (27). It is thought that the ability of non-HLA antibodies to mediate allograft injury may be associated with their affinity and strength (titer), target specificity, the intensity of target antigen, and synergy with donor-specific HLA antibodies.

The initial studies regarding Ang showed that Ang-1 stabilized newly formed vessels and reduced vascular permeability when the Tie-2 receptor of Ang-2 blocked Ang-1 activation. On the other hand, current studies included in the literature have reported that Ang-2 can directly induce Tie-2, and both Ang-1 and Ang-2 may be pro-inflammatory. Ang/Tie-2 biology is modified by vascular endothelial growth factor and Tie-1, which is a receptor associated with vascular endothelial growth factor. In healthy individuals, Tie-1 and Tie-2 are expressed in glomerular endothelium, while Ang-1 is expressed in podocytes. In vitro studies have shown that exogenous Ang-l increases the formation of capillary vessels in developing glomerules (25). In some studies on diabetic glomerulopathy and immune-mediated glomerulonephritis, it has been reported that glomerular Ang-2 expression is increased in these diseases (24, 28). In light of these data, it was presumed that Ang-2 might have important roles in the pathobiology of glomerular disease.

The literature does still not involve sufficient experimental data to definitely associate Angs with in-vivo glomerular functions. Thus, it will be useful to examine the effects of the downregulation of Ang-1 levels in healthy animals and the effects of the downregulation of Ang-2 in glomerular disease in future studies.

Although Ang-2 is known to be highly effective in endothelial dysfunction, it is unclear whether it is associated with the progression of renal dysfunction in patients with CKD. In our study, there was a positive correlation between the anti-HLA antibody loads of the patients on the kidney transplant waiting list with the diagnosis of end-stage renal disease and the serum Ang-2 levels of the same patients, and a statistically significant Ang-2 level in patients with a PRA positivity rate of 50% or higher significant increase was found. This finding suggests that Ang-2 may have an important role in the progression of CKD and may be effective in predicting graft survival after transplantation. Further studies will be required to evaluate the pathogenic role of Ang-2 in renal progression and to establish beneficial kidney function by targeting Ang-2.

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