

# Plasma Angiogenin and Vascular Endothelial Growth Factor A Among Hemodialysis Patients

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**Introduction.** Angiogenesis plays a role in the pathogenesis of coronary heart disease (CHD) and diabetes mellitus (DM) pathology, and certain angiogenic factors are increased by inflammation. The aim of this study was to evaluate plasma angiogenin and vascular endothelial factor A (VEGFA) levels in hemodialysis patients, as well as the effect of CHD, DM, and inflammation on these markers.

**Materials and Methods.** Sixty-six hemodialysis patients were enrolled in the study, of whom 22 (33.3%) suffered from CHD, 22 (33.3%) from DM, and 28 (42.4%) from inflammation. They were compared with 24 healthy volunteers. Plasma angiogenin and VEGFA were assessed by means of enzyme-linked immunosorbent assay, and serum C-reactive protein was measured with an immunoturbidimetric method. These markers were compared between hemodialysis patients with and without CHD, DM, and inflammation.

**Results.** Compared to healthy volunteers, plasma angiogenin was significantly higher in hemodialysis patients ( $263.57 \pm 65.95$  ng/mL versus  $499.15 \pm 175.68$  ng/mL;  $P < .001$ ). Similarly, plasma VEGFA was markedly increased in hemodialysis patients (median, 60.50 pg/mL; range, 280 pg/mL), compared to healthy volunteers (median, 28.84 pg/mL; range, 59.40 pg/mL;  $P < .001$ ). Neither angiogenin nor VEGFA levels differed significantly between hemodialysis patients with and without CHD, DM, or inflammation.

**Conclusions.** Plasma angiogenin and VEGFA levels are markedly increased in hemodialysis patients, but not associated with CHD, DM, or inflammation among hemodialysis patients.

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## INTRODUCTION

The prevalence of cardiovascular disease (CVD) in hemodialysis patients is extremely high. Cardiovascular disease, mainly coronary heart disease (CHD), is responsible for approximately 50% of deaths in hemodialysis patients and the CVD mortality in this population is 15 to 30 times higher than the age-adjusted CVD mortality in the

general population.<sup>1,2</sup> Certainly, one of the reasons for increased incidence of CHD in hemodialysis patients is the coexistence of various comorbid conditions. Diabetes mellitus (DM) is frequent among hemodialysis patients, and it is a well-known risk factor for CHD in both general population and hemodialysis patients.<sup>3</sup> Hemodialysis could also be considered as an inflammatory condition,<sup>4</sup> and

inflammation is known to increase cardiovascular risk in general population, and in hemodialysis patients as well.<sup>5,6</sup>

However, there is an apparent different relationship, called “reverse epidemiology,” between numerous known risk factors established in general population, such as high cholesterol, hypertension, and obesity and outcomes in hemodialysis patients.<sup>7</sup> Additional risk factors, such as vascular calcification due to aberrant calcium and phosphorous metabolism or abnormal nitric oxide metabolism in hemodialysis patients have also been identified.<sup>8,9</sup> The research for CHD pathogenesis and related markers in hemodialysis patients continues.

Angiogenesis plays a significant role in the pathogenesis of CHD; certain angiogenic factors are increased by inflammation.<sup>10,11</sup> There are studies that support a role for vascular endothelial growth factor A (VEGFA) in CVD and the interplay with oxidative stress and inflammation in hemodialysis patients.<sup>12-15</sup> Vascular endothelial growth factor A is one of the most potent and most studied angiogenic factors. It stimulates extracellular matrix degradation, proliferation, migration, and tube formation of endothelial cells and finally regulates vascular permeability by interfering with nitric oxide metabolism.<sup>16</sup>

Plasma angiogenin is a member of the *ribonuclease* superfamily. It is a normal constituent of the circulation and vasculature that rarely undergoes proliferation, but in some physiological and pathological conditions, its levels increase in blood, promoting neovascularization. Angiogenin binds membrane actin and induces basement membrane degradation. It affects endothelial cell proliferation by binding to a cell membrane receptor and it is translocated into the nucleus of the target cells enhancing ribosomal RNA transcription and protein synthesis.<sup>17,18</sup> Importantly, through the latter mechanism, angiogenin is necessary for angiogenesis induced by other angiogenic factors, including VEGFA.<sup>19</sup> Interestingly, angiogenin plays a role in the pathogenesis of CHD and DM, and it is increased by inflammation.<sup>17,18</sup> However, to our knowledge its role in the above situations in hemodialysis patients has not been evaluated yet.

In the present study, plasma levels of angiogenin and VEGFA were assessed in hemodialysis patients with and without CHD, DM, and inflammation.

## MATERIALS AND METHODS

### Patients

Sixty-six hemodialysis patients and 24 healthy volunteers derived from 2 hemodialysis units personnel participated in the study. The patients group was divided into 2 subgroups based on a diagnosis of CHD, confirmed with coronary angiography. If symptoms of CHD developed during the study period, the patients would be categorized in the CHD group. The patients were on regular hemodialysis with polysulfone low-flux dialysis membranes and bicarbonate buffer for 4-hour sessions, 3 times per week, for at least 1 year prior to the study. None of the patients or healthy volunteers suffered from any infection, malignancy or autoimmune disease, and none of the patients was receiving cytotoxic drugs, corticosteroids, or nonsteroidal anti-inflammatory drugs. Informed consent was obtained from each individual enrolled into the study and the hospital's ethics committee approved the study protocol.

### Methods

Blood samples were drawn before the start of the second dialysis session of the week. The samples were centrifuged and the harvested serum and platelet poor plasma were stored at -80°C. Plasma angiogenin and VEGFA were measured by means of the commercially available enzyme-linked immunosorbent assay kits (Quantikine Human ANG Immunoassay and Quantikine Human VEGFA Immunoassay, R&D Systems Europe, Abington, UK). Serum C-reactive protein (CRP) was measured with an immunoturbidimetric method in a Cobas Integra 400 automatic analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The cutoff of 5 mg/L was used for CRP in order to detect inflammation in hemodialysis patients.

### Statistical Analyses

The 1-sample Kolmogorov-Smirnov test was used for evaluating the normality of the variables. The angiogenin variable was normally distributed, and therefore, the independent *t* test was used for comparisons between the various groups, and the results were expressed as mean ± standard deviation. On the contrary, the VEGFA value was not normally distributed, and therefore, the nonparametric Mann-Whitney U test was used for comparisons between the various groups, and

the results were expressed as median (range). A *P* value less than .05 was considered significant. Because many hemodialysis patients suffered from more than one of the evaluated conditions (CHD, DM, and inflammation) multivariate analysis was performed with the angiogenin or the VEGFA as the dependent variable and the above conditions as the independent variables.

## RESULTS

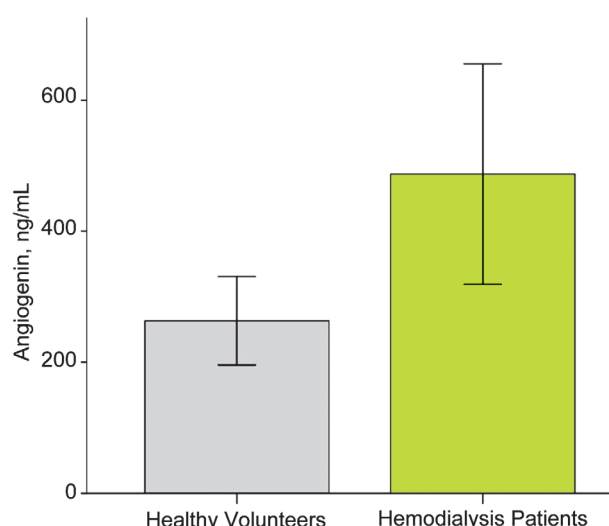
### Baseline Characteristics

Sixty-six hemodialysis patients (mean age,  $61.2 \pm 12.5$  years) and 24 healthy volunteers (mean age,  $57.0 \pm 8.6$  years) completed the study. The two groups did not differ significantly regarding age ( $P = .13$ ). All of the patients were anuric and the cause of end-stage renal disease was diabetes mellitus in 22 patients (33.3%), primary glomerulonephritis in 20 (30.3%), obstructive nephropathy in 4 (6.1%), hypertension in 4 (6.1%), interstitial nephritis in 4 (6.1%), autosomal dominant polycystic kidney disease in 2 (3.0%), Alport syndrome in 1 (1.5%), and unknown in 9 (13.6%).

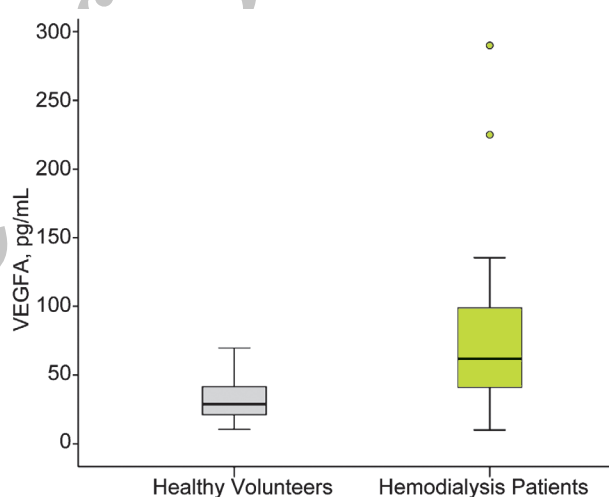
Of the 66 patients, 22 (33.3%) suffered from CHD. The two groups of the patients did not differ significantly regarding age ( $62.8 \pm 9.5$  versus  $60.5 \pm 13.7$  years,  $P = .48$ ). Twenty-two of the hemodialysis patients (33.3%) had DM. There was no significant difference between diabetic and nondiabetic hemodialysis patients regarding age ( $65.3 \pm 7.1$  group versus  $59.3 \pm 14.1$  years,  $P = .08$ ). Twenty-eight hemodialysis patients (42.4%) were identified to have high CRP values. There was no significant difference between hemodialysis patients with and without inflammation regarding age ( $62.9 \pm 12.7$  years versus  $60.1 \pm 12.4$  years,  $P = .35$ ).

### Plasma Angiogenin and Vascular Endothelial Growth Factor A

Compared to healthy volunteers, plasma angiogenin was significantly higher in the hemodialysis patients ( $499.15 \pm 175.68$  ng/mL in the hemodialysis patients and  $263.57 \pm 65.95$  ng/mL in the healthy volunteers,  $P < .001$ ; Figure 1). Similarly, plasma VEGFA was markedly increased in hemodialysis patients; The median VEGFA was 60.50 pg/mL (280 pg/mL) in the hemodialysis patients and 28.84 pg/mL (59.40 pg/mL) in the healthy volunteers ( $P < .001$ ; Figure 2).



**Figure 1.** Plasma levels of angiogenin in hemodialysis patients and healthy volunteers.



**Figure 2.** Plasma levels of vascular endothelial growth factor A (VEGFA) in hemodialysis patients and healthy volunteers.

### Plasma Angiogenin and Vascular Endothelial Growth Factor A and Coronary Heart Disease Among Hemodialysis Patients

Plasma angiogenin did not differ between the hemodialysis patients with and without CHD ( $490.46 \pm 126.01$  ng/mL versus  $502.93 \pm 194.50$  ng/mL, respectively;  $P = .79$ ). Plasma VEGFA levels were not significantly different either between these two subgroups. The median VEGFA was 58 pg/mL (143 pg/mL) in the hemodialysis patients with CHD and 57 pg/mL (280 pg/mL) in the hemodialysis patients without CHD ( $P = .80$ ).

### Plasma Angiogenin and Vascular Endothelial Growth Factor A and Diabetes Among Hemodialysis Patients

Plasma angiogenin levels did not differ between hemodialysis patients with and without DM ( $479.64 \pm 201.34$  ng/mL versus  $508.91 \pm 162.99$  ng/mL, respectively;  $P = .53$ ). There were no differences in VEGFA levels between diabetic and nondiabetic hemodialysis patients, either. The VEGFA median value was 60 pg/mL (143 pg/mL) in diabetics and 58 pg/mL (280 pg/mL) in nondiabetics ( $P = .67$ ).

### Plasma Angiogenin and Vascular Endothelial Growth Factor A and Inflammation Among Hemodialysis Patients

Plasma angiogenin levels did not differ between the hemodialysis patients with a serum CRP level higher than 5 mg/L and those with lower values ( $515.95 \pm 186.64$  ng/mL versus  $488.23 \pm 169.70$  ng/mL, respectively;  $P = .54$ ). Likewise, plasma VEGFA did not differ between hemodialysis patients with a serum CRP higher than 5 mg/L (median, 61 pg/mL; range, 143 pg/mL) and those with lower values (median, 56 pg/mL; range, 280 pg/mL;  $P = .73$ ).

### Multivariable Analysis

The linear regression analysis confirmed that CHD, DM, and inflammation did not affect plasma angiogenin levels in the hemodialysis patients (adjusted  $R^2 = -0.032$ ,  $P = .80$ ). The standardized coefficient (beta) was 0.003 for CHD ( $P = .98$ ), -0.102 for DM ( $P = .44$ ), and 0.101 for inflammation ( $P = .46$ ). Similarly, multivariable analysis confirmed that CHD, DM, and inflammation did not affect plasma VEGFA levels in the hemodialysis patients (adjusted  $R^2 = -0.023$ ,  $P = .67$ ). Beta was -0.028 for CHD ( $P = .83$ ), -0.111 for DM ( $P = .40$ ), and -0.089 for inflammation ( $P = .511$ ).

### DISCUSSION

The aim of the present study was to evaluate plasma angiogenin and VEGFA levels in hemodialysis patients and the influence of CHD, DM and inflammation. Compared to healthy volunteers both angiogenin and VEGFA were markedly increased in hemodialysis patients. Thus our results confirmed previous studies that detected increased circulating angiogenin and VEGFA levels in hemodialysis patients.<sup>14,20</sup> Because both angiogenin and VEGFA have been implicated in

the pathogenesis of CHD, DM pathology and are associated with inflammation,<sup>10,11</sup> we evaluated if their increased levels in hemodialysis patients are influenced by the coexistence of CHD, or DM, or inflammation, situations that are very common in this population.

Angiogenin levels did not differ between hemodialysis patients with or without CHD. To our knowledge, there are no other studies in hemodialysis patients that evaluate angiogenin levels in hemodialysis patients with or without CHD. The VEGFA levels did not differ between hemodialysis patients with or without CHD as well. This contradicts the results of a previous study, which showed that serum VEGFA is associated with left ventricular dysfunction and mortality in hemodialysis patients,<sup>12</sup> as well as with a study that showed increased plasma VEGFA levels in hemodialysis patients with CVD.<sup>14</sup> However, others also failed to detect difference in serum VEGF levels in hemodialysis patients with or without ischemic heart disease.<sup>13</sup> One limitation of two of the above three studies is that they measured serum VEGF, since a significant and highly variable platelet-mediated secretion of VEGFA during the clotting process has been reported.<sup>21</sup>

Although both angiogenin and VEGFA are involved in the pathogenesis of atherosclerosis and in the physical history of CHD,<sup>10,11</sup> there is controversy regarding their exact role. First, it is believed that angiogenesis through the development of collateral vessels could ameliorate ischemia in a low-perfused tissue. Clinical trials using VEGFA have been performed to this direction.<sup>11</sup> On the other hand, a population based study showed only a weak correlation between plasma VEGFA levels and cardiovascular risk factors, and in multivariate analysis no relation to intima media thickness of the carotid arteries.<sup>22</sup> Additionally, some authors support that atherosclerotic vessels often present intra-plaque angiogenesis, a phenomenon that has been hypothesized to contribute to progression and eventual rupture of coronary artery lesions.<sup>23</sup> Indeed, studies showed that both circulating angiogenin and VEGFA levels did not differ significantly between healthy subjects and patients with stable CHD, but their levels markedly increased in case of plaque rupture and myocardial infarction.<sup>24,25</sup> In the cohort of our hemodialysis patients, stable CHD predominated, and this could

partially explain the lack of difference in plasma angiogenin and VEGFA levels between patients with CHD and those without CHD.

The VEGFA is increased in children with type 1 DM and it is further increased in case of diabetic retinopathy, which is characterized by neovascularization.<sup>26</sup> On the other hand, serum angiogenin has been found decreased in patients with type 2 DM.<sup>27</sup> The last authors suggest that low angiogenin levels could contribute to the known in DM reduced collateralization in ischemic tissues, which causes impaired wound healing, exacerbation of peripheral limb ischemia, and a threefold to fourfold increase in cardiac mortality in comparison with nondiabetics.<sup>28,29</sup> Thus, both neovascularization and impaired angiogenesis coexist and play role in DM pathology. In case of hemodialysis patients, we did not find difference in the levels of both angiogenic factors between patients with or without DM. To our knowledge the impact of DM on angiogenin and VEGFA levels in hemodialysis patients has not been evaluated before.

Finally, we evaluated the impact of inflammation on plasma angiogenin and VEGFA levels. Population based studies have shown that both circulating angiogenin and VEGFA levels are related to serum markers of inflammation.<sup>22,30</sup> The same was confirmed for VEGFA in patients with DM.<sup>26</sup> There is also direct experimental evidence that angiogenin is regulated in vivo as an acute phase protein.<sup>31</sup> To our knowledge, in hemodialysis patients there are no data about the impact of inflammation on angiogenin levels, whereas regarding VEGFA the available studies are inconclusive. Some studies showed that serum VEGFA level is associated with markers of inflammation,<sup>12,15</sup> whereas other studies did not find relation.<sup>13,32</sup> In the present study neither angiogenin, nor VEGFA levels differ between hemodialysis patients with or without inflammation.

Because many hemodialysis patients suffered from more than one of the evaluated conditions (CHD, DM and inflammation) multivariate analysis was also performed. Interestingly, multivariate analysis was also failed to reveal dependence of angiogenin or VEGFA plasma levels from any of three studied conditions.

The lack of difference in plasma angiogenin and VEGFA levels between hemodialysis patients

with or without CHD, DM or inflammation found in the present study does not necessary excludes an etiological and possibly bidirectional interplay between these angiogenic factors and atherosclerosis, DM pathology and inflammation. The accumulation of these angiogenic factors because of renal failure per se, which may contribute to their increased plasma values in hemodialysis patients, could mask differences owned to the studied situations. Indeed, in predialysis patients plasma VEGFA showed a strong inverse relationship with estimated glomerular filtration rate.<sup>33</sup> Interestingly, in a study in peritoneal dialysis patients, plasma VEGFA levels were strongly dependent on the residual kidney function. Patients with residual kidney function greater than 2.0 mL/min were characterized by significantly lower levels of VEGFA compared to those without residual kidney function (< 2.0 mL/min). Furthermore, the small number of the subjects participated in each subgroup is a limitation of the present study, which has to be considered in the interpretation of the results.

Other roles of the increased angiogenin and VEGFA levels in hemodialysis patients could not be excluded. For example, increased angiogenin levels could play a role in decreased function of neutrophils,<sup>34</sup> and consequently in increased susceptibility to bacterial infections observed in hemodialysis patients.<sup>35</sup> Furthermore, considering the need for neovascularization for cancer growth and metastasis,<sup>10</sup> increased angiogenic factors levels could contribute to the increased by 10% to 80% risk for cancer in hemodialysis patients.<sup>36</sup>

## CONCLUSIONS

Plasma angiogenin and VEGFA are markedly increased in hemodialysis patients, but did not differ between hemodialysis patients with or without CHD or DM or inflammation. Although the last, if re-confirmed in larger studies, may excludes their use as clinically relevant markers, an etiological and possibly bidirectional interaction between these angiogenic factors and the above situations could not be excluded simply by assessing their plasma levels. The possible role of the increased angiogenin and VEGFA levels in other pathological entities also needs evaluation.

## CONFLICT OF INTEREST

None declared.

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