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Asymmetric dimethylarginine and whole blood viscosity in renal failure

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Abstract

BACKGROUND—Renal failure is a disease with accelerated atherosclerosis beginning with endothelial cell dysfunction. Factors affecting endothelial cell dysfunction include whole blood viscosity (WBV) and asymmetric dimethylarginine (ADMA). The relationship in controls and renal failure was determined.

METHODS—51 subjects, 20 controls, 11 renal transplant recipients, 10 chronic kidney disease and 10 end-stage renal disease patients had blood samples drawn for WBV, Hematocrit, and ADMA. WBV was measured at various shear rates from 10 s⁻¹ to 780 s⁻¹ at 37°C. Hematocrit using CritSpin, and ADMA was assayed using an ELISA method. The significance between groups was compared by boxplots and analysis of variance. Linear relationships were shown by regression lines and correlation coefficients.

RESULTS—ADMA was elevated in all groups with renal failure when compared to controls ($p < 0.05$). Control subjects showed a positive correlation between ADMA and WBV, while those who received a renal transplant had a negative correlation ($p < 0.05$). The difference in ADMA comparing pre-dialysis to post-dialysis conditions was positive ($p < 0.05$).

CONCLUSIONS—The positive relationship between WBV and ADMA in controls is a novel finding and allows for comparison with other groups. This relationship is dramatically altered in renal failure.

Keywords

Asymmetric dimethylarginine; endothelial cell; nitric oxide; renal failure; viscosity

Disclosure

The authors have no competing interests to disclose.

1. Introduction

As part of the regulation of the microcirculation, nitric oxide (NO) is released in response to endothelial wall shear stress [22]. Asymmetric dimethylarginine (ADMA) is a potent competitive inhibitor of NO. The mechanism appears to be inhibition of NO synthesis by specific effects on nitric oxide synthetase (NOS) [24]. We reasoned (Hypothesis 1) that a potential counter-regulator of NO, ADMA, might be released by the same physiologic stimulus that releases NO. If this were true, then ADMA production must be positively correlated with endothelial cell wall shear stress in normal people. It is impractical to measure shear stress directly in normal people. However, whole blood viscosity (WBV) is known to correlate positively with shear stress [9] and is therefore a serviceable gauge.

Regulation of the microcirculation is abnormal in CKD, hemodialysis, and renal allograft recipient patients [2]. Inadequate NO contributes to development of both CKD and vascular disease [6]. ADMA, a well known risk factor linked to accelerated atherosclerosis, is increased in patients with kidney disease, because of reduced enzymatic degradation of dimethylaminohydrolase (DDAH) and decreased excretion [7, 20]. Therefore, we reasoned that (Hypothesis 2) ADMA regulation by WBV might be abnormal in these patients. If so, ADMA would not correlate positively with WBV.

Vascular disease beginning with endothelial cell dysfunction is the leading cause of mortality for patients receiving hemodialysis. ADMA, known to occur at very high levels in patients with end-stage renal disease (ESRD), contributes to vascular disease [27]. Previous reports have inconsistent results regarding the effects of hemodialysis clearance for ADMA [17]. Because ADMA has a small molecular weight, we reasoned that (Hypothesis 3) ADMA would be cleared with dialysis.

2. Methods

2.1. Experimental design

1). Test the hypothesis that ADMA is regulated by WBV in normal people. Using paired measurements of ADMA and WBV in a group of people without CKD or any systemic disease, we determined whether ADMA and WBV were positively correlated using simple regression analysis. 2). In groups of patients with CKD, ESRD receiving hemodialysis, and renal allograft recipients and using similar paired measurements of ADMA and WBV, we determined whether ADA and WBV were correlated. 3). In a group of patients receiving hemodialysis, we obtained pairs of values for WBV and ADMA prior to and at termination of dialysis and determined whether they differed using paired *t*-tests.

2.2. Patients and normal subjects

A total of 51 subjects (20 controls, 11 transplant recipients, 10 patients with CKD and 10 patients with ESRD) were studied (Table 1). We choose young (age 22.8 ± 0.6 years) men and women (10 each) with no disease who were receiving no significant medications. By choice, they are considerably younger than our patient groups because they are intended to test Hypothesis 1 and are not specifically compared to the ESRD, transplant, and CKD patients as a test of either of our hypotheses. What we wanted were people who could

ideally represent the normal population in health. All the patients in the renal transplant group received a renal transplant and were taking similar immunosuppressive medication (Tacrolimus, Mycophelate and Prednisone). Hypertension was common in transplant recipients as 10/11 were taking anti-hypertensive meds including calcium channel blockers in 7; angiotension-converting-enzyme-inhibitors in 2; and beta-blockers in 2. The mean time of renal transplant was 3.6 years with range of 2 months to 10 years. 6 subjects had received a deceased donor, 4 a living related, and one a living unrelated donor kidney. One of the subjects in the CKD group was receiving Erythropoietin therapy. All ESRD patients were receiving hemodialysis three times a week with an achieved single pool Kt/V of 1.2. Patients were dialyzed using the Gambro Phoenix dialysis machine and Fresenius Polysulfone Opiflux filter. The high flux dialyzer used varied from F-160 to F-200, depending on BMI. The dialysate flow rate was 800 mL/min. A standard bicarbonate bath of 35 mEq/L was used to maintain patient pH between 7.3 and 7.5 during dialysis. Seven subjects in the ESRD group were receiving Erythropoietin (2200 units – 14,300 units). This study was submitted to, and approved by the Institutional Review Board at the University of Chicago (protocol 11-0557) and by Davita Dialysis for patients with ESRD. There was approval by the Institutional Review Board at Illinois Institute of Technology for the control subjects (protocol 2010-060). Informed written consent was obtained from each participant before trial onset.

2.3. Protocol

Subjects in the control, transplant and CKD study groups had blood samples obtained by routine venipuncture. Samples from subjects with ESRD were obtained from the patient's access (central venous catheter, graft or fistula) immediately before and after hemodialysis. All blood was collected in 4.5 mL blue-stopper tubes containing 3.2% buffered sodium citrate. Blood samples were stored at 4°C and processed for WBV and Hct within 4–6 hours of collection.

2.4. Laboratory measurements

Whole blood viscosity was measured using Brookfield programmable DV-II + cone and plate viscometer. The viscometer was calibrated with 600 µl of standard oil (procured from Brookfield Engineering, Middleboro, MA) before starting the measurements. The WBV was measured at various shear rates from 10 s⁻¹ to 780 s⁻¹ at 37°C. The shear rates were chosen between 10% to 100% of torque. Three measurements for each shear rate were determined and the results recorded. The average variance between samples was 0.001%–1.9%. Each sample had the hematocrit (Hct) measured using CritSpin capillary tube micro centrifuge (Stat Spin, Norwood, MA). The remaining blood from the sample was centrifuged for 15 minutes at 1500 xg using the Eppendorf Centrifuge 5810 R. The plasma was separated and stored in aliquots at –80°C for ADMA assay. An ELISA kit (EUROIMU US, Jersey City, NJ) was used to assay ADMA [21].

2.5. Statistical analysis

ADMA and WBV values were compared in the four groups (Control, ESRD, Transplant, and CKD) via boxplots and analysis of variance (ANOVA). Tukey's test was used to examine all pair wise comparisons of ADMA and WBV. Pre- and post-dialysis ADMA and

WBV values in ESRD patients were compared via Wilcoxon signed rank tests. Two general linear models with ADMA as dependent variable and gender, age, group, and either WBV or Hct as predictor variables were used to examine the relationships between ADMA and either WBV or Hct. The models included WBV-group and Hct-group interaction terms, respectively. Linear mixed effects regression models of pre- and post- dialysis ADMA, adjusted for pre-and post- dialysis WBV, time (post vs. pre), and either age or intra-dialytic weight gain (IDWG) were used to analyze effects of dialysis. Age and IDWG were analyzed separately due to significant negative correlation between age and IDWG. Pairwise scatter plots and Pearson correlation analysis of WBV and Hct (not shown) revealed evidence of significant positive linear relationships between WBV and Hct within each study group. Adjusting for both of these correlated variables in a single model was not possible due to risk of co-linearity and model instability. *P*-values were assessed at the 5% significance level. All statistical analyses were performed in R version 2.13.1.

3. Results

3.1. Univariate mean value and frequency comparison

The controls were younger than the transplant and CKD groups (Table 1). ADMA values in ESRD, transplant, and CKD patients were significantly higher than control subjects (Fig. 1, left panel). WBV values did not differ significantly among the groups (Fig. 1, right panel) ($p > 0.05$). We computed mean WBV at various shear rates ranging from 10 s^{-1} to 780 s^{-1} at 37°C in all 51 subjects demonstrating expected behavior of the blood samples at different shear rates (Fig. 2). 95% confidence intervals for pairwise mean group differences in ADMA exclude zero for most pairs (Fig. 3), suggesting that there were significant intra-group differences. Overall, ADMA values of patients exceeded normal whereas WBV values did not.

3.2. Hypothesis 1

In a regression analysis with adjustment for age and sex, ADMA varied directly with WBV in controls (open square) (Fig. 4); (95% CI for β : (0.016, 0.03); $p = 0.01$). We obtained similar results when we log-transformed WBV to attenuate excess variability in WBV (95% CI for log-scale β : (0.087, 0.553); $p = 0.01$).

3.3. Hypothesis 2

In patients with a transplanted kidney (Fig. 5, solid triangles), using a regression analysis with adjustment for age and sex, ADMA varied inversely with WBV; (95% CI for β : (0.315, 0.505); $p < 0.001$). In patients with CKD (Fig. 5, gray inverted triangles) or those with ESRD (Fig. 5, solid circle), ADMA and WBV were not related; (95% CI for β : (−0.177, 0.117) and (−0.256, 0.136), respectively; $p > 0.05$). Given the lack of significant regression slopes for CKD and ESRD, we did not compare them to transplant.

3.4. Effects of hemodialysis

Although unrelated to our two hypotheses, we asked if hemodialysis might alter ADMA level (METHODS). Mean difference in ADMA in going from pre-dialysis to post-dialysis conditions was positive (0.16 ± 0.02), and 95% confidence intervals for the ADMA

difference (0.11, 0.20) exclude zero (Fig. 6, *left panel*). This suggests that ADMA usually increased after dialysis in ESRD patients (Wilcoxon signed rank test, $p = 0.002$). A similar analysis revealed a significant increase in WBV (0.72 ± 0.25 ; 95% CI: (0.16,1.28); $p = 0.002$). (Fig. 6, *right panel*). In a linear mixed effects regression analysis of pre- and post-dialysis ADMA, adjusted for pre- and post-dialysis WBV, time (post vs. pre), and either age or interdialytic weight gain (IDWG), ADMA and WBV were not related (pNS) (data not shown). In other words, the increase in ADMA is not accounted for by the increase in WBV nor by effects of time, age, or IDWG.

4. Discussion

Our primary goal was to test the claim that ADMA release might be regulated in the same manner as NO: via increase in wall shear stress [25]. As a proxy for wall shear stress, we used WBV which has been thoroughly tested for use in this manner [9]. Our experiment was designed so that a failure to find a positive correlation between ADMA and WBV would falsify our hypothesis. We found a highly significant positive correlation, meaning that the hypothesis stands for the moment as supported.

The positive relationship between WBV and ADMA has not been previously reported. This relationship is of interest as both affect the production of NO by endothelial cells and NO has profound influence on the microcirculation [18]. Increased WBV and resultant shear stress cause mechanical pressure on endothelial cells which stimulate the release of NOS [23]. NOS causes generation of NO which has direct and indirect effects to relax smooth muscle while inhibiting platelet aggregation, monocyte adhesion, smooth muscle cell proliferation, and LDL oxidation, all important physiologic processes which are beneficial to enhance blood flow [8, 14]. The findings in this study are the first to support that ADMA, an inhibitor of NO, maybe regulated in response to WBV.

Our secondary goal was to test if ADMA was regulated via wall shear stress in three groups of patients with differing levels of clinical renal impairment. Among transplant patients, we found a strong and inverse correlation between ADMA and WBV, meaning that regulation of ADMA is abnormal. Post transplant there is usually a significant hemodynamic improvement and stability as shown by arterial dilation up to 28 days after transplant with an associated decrease in ADMA [26]. Others have reported an increase in ADMA possibly due to a decrease in methylation in renal transplant recipients when compared to controls [17]. In a retrospective review, ADMA has been found to be a risk factor for renal transplant rejection [1]. Medications commonly prescribed in the post transplant period affect the level of ADMA. While Tacrolimus reduces NOS function [10], Amlodipine and Valsartan decrease ADMA [4]. The interplay of immunosuppression and anti-hypertensive medications may account for the abnormal relationship between WBV and ADMA. This can only be studied by direct experimentation.

In CKD and ESRD, ADMA values were much higher than normal and unrelated to WBV. Taken together with our findings in transplant patients, we are forced to conclude that disordered ADMA regulation is widespread in the practice of nephrology. There is considerable evidence that NOS inhibition causes systemic and glomerular hypertension,

glomerular and tubular injury, and proteinuria [15]. It is likely that CKD-induced NO deficiency as a result of elevated ADMA contributes to the progression of renal disease and accelerated atherosclerosis, a common finding in patients with renal failure from any cause [11].

Our third goal was to perform our own experiment to test the effect of hemodialysis on the level of ADMA. We found a consistent and significant increase in ADMA and WBV post dialysis. Hemodialysis itself has been shown to increase WBV and NO activity [13]. WBV increase after dialysis is in part due to ultrafiltration [12] but in our regression analysis WBV did not account for the increase in ADMA. Previous reports that show ADMA levels increase, decrease or remain unchanged post dialysis may differ from our experiment technically [17, 19]. Several factors affect the clearance of ADMA by dialysis including: protein binding, pH of dialysate, and timing of the samples [17]. The significant increase in ADMA we observed post dialysis is consistent with either higher production rates of ADMA during hemodialysis, decreased activity of DDHA or re-equilibration. Confirmation of this finding in future studies and the biological significance are important given the deleterious effects of ADMA in renal failure. If there was confirmation of increased clearance of ADMA with dialysis that would be beneficial for patients as the treatment itself would clear this harmful protein.

Our study has limitations. There was an apparent age difference in controls, and ADMA is known to increase with age [5]. No one to date has tested if ADMA correlates with WBV in elderly patients. Our study did not address diabetes, a well known disease with atherosclerosis. NO itself was not quantitated to validate our findings. While these may be investigated in the future, to our knowledge, we are the first to show the relationship of WBV to ADMA in controls and those with renal failure. Therapeutic trials to increase WBV and decrease ADMA may improve the outcomes for patients with renal failure. WBV could be increased or decreased by adjusting Hematocrit, which is easily done in renal failure by administration of erythropoietin. ADMA could be decreased by administration of the amino acid Arginine or treatment of hypertension with selective medications, such as Nebivolol and Bidil, known to improve NO activity in blood vessels [16].

In conclusion, CKD is a complex disease that leads to a high prevalence of vascular complications. Impairment in the microvascular blood flow beginning at the endothelial cell contributes to these conditions. ADMA and WBV are factors that determine blood flow with significant effect on the production of nitric oxide. Future investigation to understand the molecular mechanisms of the generation of nitric oxide in response to shear stress and relationship to ADMA and its metabolites have important implications for future research.

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References

1. Abedini S, Meinitzer A, Holme I, Marz W, Weihrauch G, Fellstrom B, Jardine A, Holdaas H. Asymmetrical dimethylarginine is associated with renal and cardiovascular outcomes and all-cause mortality in renal transplant recipients. *Kidney Int.* 2010; 77:44–50. [PubMed: 19847152]
2. Aldamiz-Echevarria L, Abdrade F. Asymmetric Dimethylarginine, endothelial dysfunction and renal disease. *Int J Mol Sci.* 2012; 11:11288–11311. [PubMed: 23109853]
3. Andrade F, Rodriguez-Soriano J, Prieto JA, Aquire M, Ariceta G, Lage S, Azcona I, Prado C, Sanjurjo P, Aldamiz-Echevarria L. Methylation cycle, arginine-creatinine pathway and asymmetric dimethylarginine in pediatric renal transplant. *Nephrol Dial Transplant.* 2011; 26:328–226. [PubMed: 20605841]
4. Aslam S, Santha T, Leone A, Wilcox C. Effects of amlodipine and valsartan on oxidative stress and plasma methylarginines in end-stage renal disease patients on hemodialysis. *Kidney Int.* 2006; 70:2109–2115. [PubMed: 17063175]
5. Assar ME, Angula J, Vallejo S, Peiro C, Sanchez-Ferrer CF, Rodriquez-Manas L. Mechanisms involved in the aging-induced vascular dysfunction. *Frontiers in Physiology.* 2012; 3:1–13. [PubMed: 22275902]
6. Baylis C. Nitric oxide deficiency in chronic kidney disease. *Am J Physiol Renal Physiol.* 2008; 42:F1–F9. [PubMed: 17928410]
7. Boger RH. Asymmetric Dimethylarginine, endogenous inhibitor of nitric oxide synthetase, explains the “L-Arginine Paradox” and acts as a novel cardiovascular risk factor. *J Nutr.* 2004; 134:2842S–2847S. [PubMed: 15465797]
8. Boger RH, Sydow K, Borlak J, Thum T, Lenzen H, Schubert B, Tsikas D, Bode-Boger SM. LDL cholesterol upregulates synthesis of Asymmetrical Dimethylarginine in human endothelial cells. *Circ Res.* 2000; 87:99–105. [PubMed: 10903992]
9. Chien S. Mechanotransduction and endothelial cell homeostasis: The wisdom of the cell. *Am J Physiol Heart Circ Physiol.* 2007; 292:H1209–H1224. [PubMed: 17098825]
10. Cook LG, Chiasson VL, Long C, Chiasson VL, Long C, Wu GY, Mitchell BM. Tacrolimus reduces nitric oxide synthetase function by binding to FKBP rather than by its calcineurin effect. *Kidney Int.* 2009; 75:719–726. [PubMed: 19177155]
11. Daix-Buxo JA, Woods HF. Protecting the endothelium: A new focus for management of chronic kidney disease. *Hemodial Int.* 2006; 10:42–48. [PubMed: 16441826]
12. Dhar P, Eadon M, Hallack P, Munoz RA, Hammes M. Whole blood viscosity: Effect of hemodialysis treatment and implications for access patency and vascular disease. *Clin Hemorheol Microcirc.* 2012; 51:265–275. [PubMed: 22337820]
13. Eiselt J, Rajdl D, Racek J, Siroka R, Trefil L, Opatrna S. Asymmetric dimethylarginine in hemodialysis, hemodiafiltration and peritoneal dialysis. *Artif Organs.* 2010; 34:420–425. [PubMed: 20633156]
14. Harrison DG. Cellular and molecular mechanism of endothelial cell dysfunction. *J Clin Invest.* 1997; 100:2153–2157. [PubMed: 9410891]
15. Katz R, Baylis C. Chronic nitric oxide inhibition model six years on. *Hypertension.* 1998; 32:958–964. [PubMed: 9856957]
16. Khawaja Z, Wilcox CS. Role of the kidney in Resistant Hypertension. *Inter J of Hyper.* 2011; 2011:Article ID 143471. 8 pages. 10.4061/2011/143471
17. Kielstein JT, Boger RH, Bode-Boger SM, Martins-Lobenotter J, Lonnemann G, Frolich JC, Haller H, Fliscar D. Low dialysance of asymmetric dimethylarginine (ADMA) – *in vivo* and *in vitro* evidence of significant protein binding. *Clin Neph.* 2004; 62:295–300.
18. Leone A, Moncada S, Vallance P, Calver A, Collier J. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. *The Lancet.* 1992; 339:572–575.
19. MacAllister RJ, Rambausek MH, Vallance P, Williams D, Hoffman KH, Ritz E. Concentration of dimethyl-L-arginine in the plasma of patients with end-stage renal failure. *Nephrol Dial Transplant.* 1996; 11:2449–2452. [PubMed: 9017621]
20. Matsuguma K, Ueda S, Yamagishi S, Matsumoto Y, Kaneyuki U, Shibata R, Fujimura T, Matsuoka H, Kimoto M, Kato S, Imaizumi T, Okuda S. Molecular mechanism for elevation of

- asymmetric dimethylarginine and its role for hypertension in chronic kidney disease. *J Am Soc Nephrol.* 2006; 17:2176–2183. [PubMed: 16807406]
21. Schulze, Wesemann R, Schwedhelm E, Sydow K, Albsmeier J, Cooke JP, Boger RH. Determination of Asymmetric Dimethylarginine (ADMA) using a novel ELISA assay. *Clin Chem Lab Med.* 2004; 42:1377–1383. [PubMed: 15576299]
22. Uematsu M, Ohara Y, Navas JP, Nishida K, Murphy TJ, Alexander RW, Nerem RM. Regulation of endothelial cell nitric oxide synthase mRNA expression by shear stress. *Am J Physiol Cell Physiol.* 1995; 269:C1371–C1378.
23. Ulker P, Meiselman HJ, Baskurt OK. Nitric oxide generation in red blood cells induced by mechanical stress. *Clin Hemorheol Microcirc.* 2010; 45:169–175. [PubMed: 20675897]
24. Valance P, Leone A, Calver A, Collier J, Moncada S. Endogenous dimethylarginine as an inhibitor of nitric oxide synthesis. *J Cardiovasc Pharmacol.* 1992; 20:S60–S62. [PubMed: 1282988]
25. Vasquez BY, Martini J, Negrete AC, Tsai AG, Forconi S, Cabrales P, Johnson PC, Intaglietta M. Cardiovascular benefits in moderate increases of blood and plasma viscosity: Experimental and clinical evidence. *Clin Hemorheol Microcirc.* 2010; 44:75–85. [PubMed: 20203362]
26. Yilmaz MI, Saglam M, Caglar K, Cakir E, Ozgurtas T, Sonmez A, Eyileten T, Yenicesu M, Acikel C, Oguz Y, Ozacn O, Bozlar U, Erbil K, Aslan I, Vural A. Endothelial functions improve with decrease in asymmetric dimethylarginine (ADMA) levels after renal transplant. *Transplantation.* 2005; 80:1660–1666. [PubMed: 16378057]
27. Zocali C, Bode-Boger SM, Mallamaci F, Benedetto FA, Tripepi G, Malatino LS, Bellanuova I, Fermo I, Frolich JC, Boger RH. Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: A prospective study. *Lancet.* 2001; 358:2113–2117. [PubMed: 11784625]

Fig. 1.

ADMA, and WBV Values for Controls, ESRD, Transplant and CKD. Values are represented as box plots with bold bar showing median and °representing outliers. Control, normal subjects; ESRD, end stage renal disease; Transplant, transplant recipient; CKD, chronic kidney disease; ADMA, asymmetric dimethylarginine; WBV, whole blood viscosity. The mean values for ADMA (μmol/L) are: ESRD (1.82 ± 0.07); transplant recipients (1.21 ± 0.25); and those with a history of CKD (1.75 ± 0.07); all exceeded normal (0.7 ± 0.06). The median values for WBV (cP) of ESRD (3.22 ± 0.31); transplant recipients (3.61 ± 0.59); those with a history of CKD (3.24 ± 0.53); did not differ from control subjects (3.62 ± 0.41).

Fig. 2.

Shear rate versus WBV by group. WBV at shear rates (10 s^{-1} to 780 s^{-1}) in 51 subjects by group. The patients with CKD are represented by a blue diamond; the patients with ESRD are represented by a red square; the control subjects are represented by a green triangle and the patients with a renal transplant are represented by a gray X. Standard error bars are represented.

Fig. 3. Pairwise mean group difference for ADMA. Values for pairwise comparison of 95% confidence intervals for ADMA. ESRD, end stage renal disease; Transplant, transplant recipient; CKD, chronic kidney disease; ADMA, asymmetric dimethylarginine.

Fig. 4. Relationship between WBV and ADMA in controls. WBV (cP) is shown on the x-axis and ADMA (μmol/L) is shown on the y-axis. The controls are represented by open squares. A positive relationship exists for controls ($p < 0.05$). ADMA, asymmetric dimethylarginine; WBV, whole blood viscosity.

Fig. 5.

Relationship between WBV and ADMA in patients with ESRD, transplant recipients and chronic renal disease. WBV (cP) is shown on the x-axis and ADMA (μmol/L) is shown on the y-axis. The patients with ESRD are represented by solid black circles, the patients with a history of renal transplant by the solid black triangles, and patients with CKD by inverted gray triangles. There was a negative relationship for transplant patients ($p < 0.05$). The relationship between WBV and ADMA is not significant for ESRD or CKD patients. In a general linear model with adjustment for age and gender, slopes were heterogeneous between the transplant patients and the normal subjects ($p < 0.001$).

Fig. 6. Individual results for ESRD patients Pre-dialysis and Post-dialysis. Individual results for ADMA and WBV pre-dialysis and post-dialysis. ESRD, end stage renal disease; ADMA, asymmetric dimethylarginine; WBV, whole blood viscosity.

Table 1

Characteristics of subjects

	ESRD	Transplant	CKD	P-value
Age (years)	28.2 ± 1.41	33.27 ± 2 ^a	63.7 ± 5.98 ^{abc}	<0.001
Men	5 (50%)	6 (54.5%)	5 (50%)	1
Caucasian	0 (0%)	2 (18.2%)	1 (10%)	0.76
African American	10 (100%)	9 (81.8%)	9 (90%)	
Other	0 (0%)	0 (0%)	0 (0%)	
Weight	100.21 ± 11.19	85.51 ± 7.45	86.11 ± 8.77	0.45
Height	170.45 ± 3.14	170.88 ± 2.14	165.49 ± 3.86	0.4
BMI (kg/m ²)	33.81 ± 2.99	29.13 ± 2.34	31.16 ± 2.67	0.47
Etiology of Renal Failure				
Diabetes	0 (0%)	2 (18.2%)	0 (0%)	0.31
Hypertension	5 (50%)	3 (27.3%)	7 (70%)	0.17
GN	4 (40%)	5 (45.5%)	1 (10%)	0.24
Other Etiology	1 (10%)	1 (9.1%)	2 (20%)	0.83
Hypertension	6 (60%)	10 (90.9%)	10 (100%)	0.058
Cardiovascular disease	0 (0%)	0 (0%)	2 (20%)	0.19
Lupus	2 (20%)	1 (9.1%)	0 (0%)	0.51
Creatinine	11.52 ± 1.07	2.02 ± 0.28 ^b	1.81 ± 0.24 ^b	<0.001
eGFR	6.9 ± 0.82	44.55 ± 8.15 ^b	42.5 ± 8.9 ^b	0.0011
Hematocrit (%)	31.86 ± 0.8 ^a	37.06 ± 1.49 ^b	38.37 ± 1.99 ^b	0.0054
Protein	7.26 ± 0.12	6.68 ± 0.32	7.29 ± 0.23	0.15

Values are means ± SE or counts (%) as appropriate. Controls age 22.8 ± 0.6 years, 10 men and 10 women. ESRD, end stage renal disease; Transplant, transplant recipient; CKD, chronic kidney disease. Superscripts denote significant differences from (a) controls, (b) ESRD, or (c) transplant recipients in Tukey's all-pairwise comparison tests.