Biomarker Analysis of Vascular Outcomes in End Stage Renal Disease

P Sweigert, V Bansal, D Hoppensteadt, J Saluk, D Syed, J Fareed
Departments of Pathology & Medicine, Loyola University Chicago, Maywood, IL, USA

Abstract

Introduction:
End-Stage Renal Disease (ESRD) presents a complex syndrome in which inflammatory and metabolic processes contribute to disease progression and development of comorbid clinical outcomes. The relevance of some of the biomarkers of inflammation and metabolic syndrome to vascular outcomes in ESRD is not clear. In order to study these relationships, biochip array technology offers a method to profile the complex plasma biomarker environment in the setting of various comorbid clinical outcomes such as Stroke or Transient Ischemic Attack (TIA), Acute Coronary Syndrome (ACS), Congestive Heart Failure (CHF), and Coronary Artery Disease (CAD).

Methods:
Plasma samples were collected from 83 ESRD patients (mean age 65) prior to hemodialysis and were profiled using biochips for metabolic and inflammatory biomarker levels. Inflammatory cytokine and Metabolic Syndrome arrays (RANDOX, Antrim, UK) were used to profile C peptide, ferritin, insulin, leptin, resistin, TNFa, PAI-1, IL1a, IL1b, IL2, IL4, IL6, IL8, IL10, VEGF, EGF, IFNG, and MCP1. Retrospective review of the medical record was performed in order to group patients based on history of Stroke or TIA, ACS, CHF, and CAD. Plasma biomarker levels were then compared between groups with and without history of each comorbidity.

Results:
Of the 83 ESRD patients, 25 (30.1%) were found to have history of Stroke/TIA, 14 (16.9%) were found to have history of ACS, 30 (36.1%) were found to have history of CHF, and 39 (47.0%) were found to have history of CAD. The patients with history of Stroke/TIA were found to have decreased plasma IFNG levels (p=0.042) and elevated plasma resistin, IL1a, and leptin levels (p=0.008, 0.021, 0.026; respectively) when compared to ESRD patients without history of Stroke/TIA. The patients with history of ACS were found to have elevated plasma IL6 levels (p=0.040) when compared to ESRD patients without history of ACS. The patients with history of CHF were found to have decreased plasma leptin levels (p=0.031) and elevated plasma IL1b levels (p=0.042) when compared to ESRD patients without history of CHF. The patients with history of CAD were found to have elevated plasma IL1a levels (p=0.049) when compared to ESRD patients without history of CAD.

Conclusions:
Profiling of multiple inflammatory and metabolic syndrome biomarkers may aid in the risk stratification of ESRD patients for cerebrovascular and cardiovascular disorders. IL1a was found to be elevated in both Stroke/TIA and CAD, whereas in Stroke, resistin, and leptin were also higher along with decreased IFNG. Interestingly, despite an increase in IL1b, leptin was decreased in CHF. These studies demonstrate that biomarker profiling of vascular comorbidities in ESRD may provide useful diagnostic and prognostic information in the management of ESRD patients.

Introduction

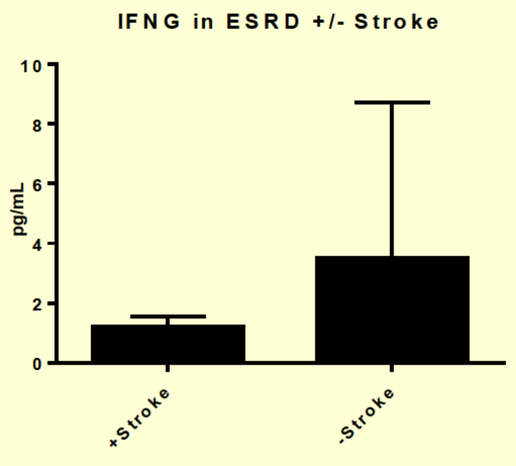
Patients with ESRD are known to have a high co-incidence of cardiovascular and cerebrovascular diseases, which in contributes a significant increase in all-cause mortality. This is due, in large part, to the fact that these patients are known to possess high numbers of traditional risk factors for vascular outcomes. However, it has been proposed that in addition to these known indicators, a complex systemic metabolic and inflammatory microenvironment exists in ESRD patients that may play a role in the pathogenesis of such comorbidities.

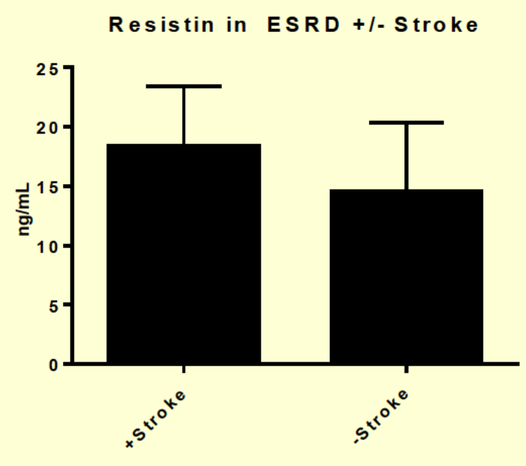
Our study examines this microenvironment in 83 ESRD patients by comparing plasma metabolic and inflammatory biomarker concentrations between groups with and without a history of a vascular comorbidity. Vascular comorbidities examined included Stroke (defined as a cerebrovascular infarction or a TIA), ACS (defined as one or more of the following: ST segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, or unstable angina), CHF (systolic, diastolic or unspecified), CAD.

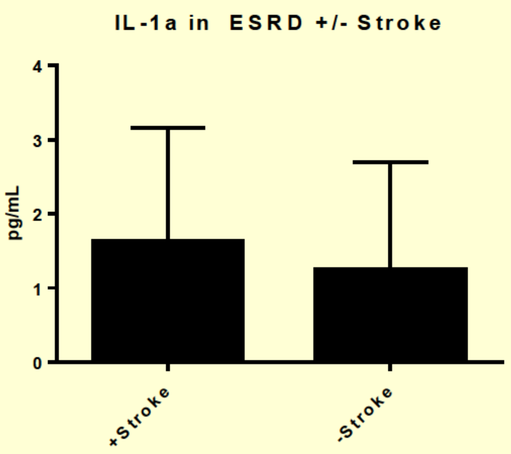
Results

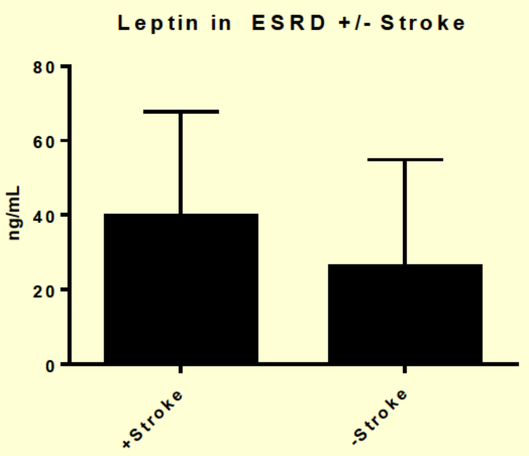
Summary of Biomarker Concentration Differences in ESRD Patients +/- Vascular Comorbidity

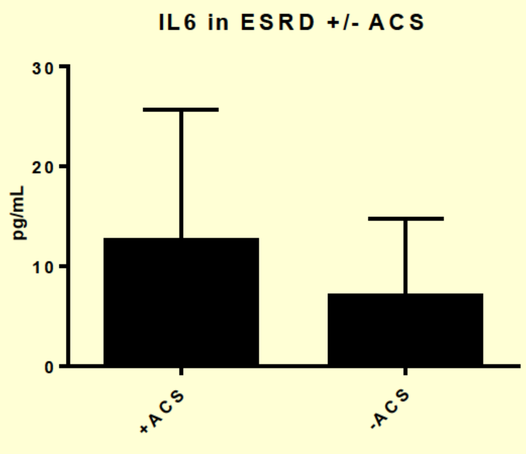
		P-value	% difference
Stroke	IFNG	0.0421	-192
	Resistin	0.0077	26.2
	IL-1a	0.0211	30.2
	Leptin	0.0264	52.0
ACS	IL-6	0.0399	79.4
CHF	Leptin	0.0311	-35.9
	IL-1b	0.0422	-15.3
CAD	IL-1a	0.0492	937

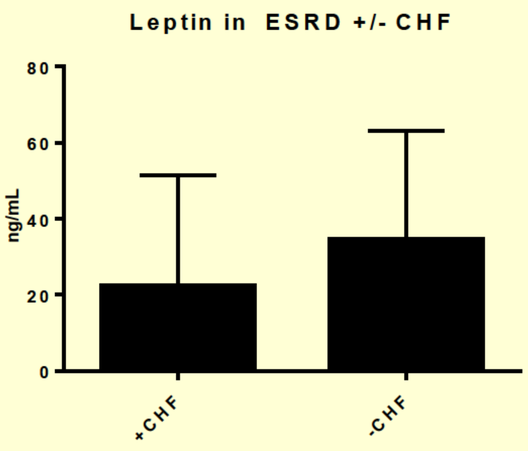


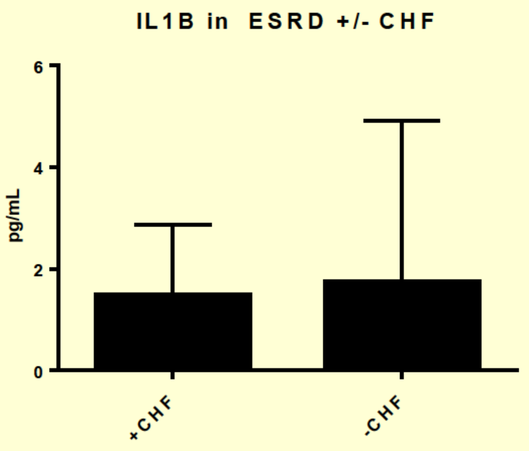


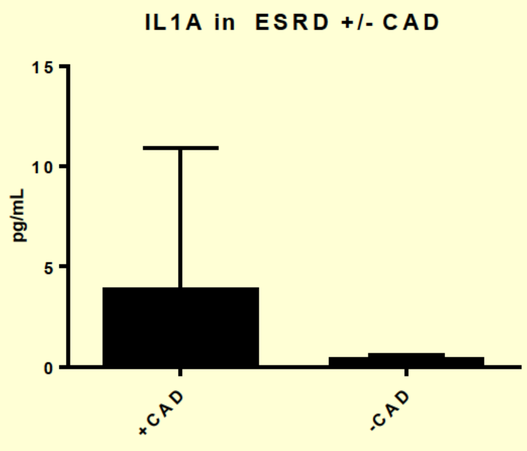












Materials & Methods

Biomarker evaluation
Under IRB approval, plasma samples were collected from 83 patients with ESRD prior to hemodialysis on November 1st and 2nd, 2013. Samples were stored at -80° C. Inflammatory and Metabolic biochips were purchased from RANDOX (Co. Antrim, Northern Ireland) to profile C peptide, ferritin, insulin, leptin, resistin, TNFa, PAI-1, IL1a, IL1b, IL2, IL4, IL6, IL8, IL10, VEGF, EGF, IFNG, and MCP1. These biomarkers were tested on 83 ESRD samples.

Retrospective Medical Record Review
The electronic medical chart records including, but not limited to: History and Physicals, Discharge Summaries, Nephrology Progress Notes, Cardiology Progress Notes, and Neurology Progress Notes from each patient were reviewed at least 10 years retrospectively for documentation of comorbid diagnoses by an attending physician. Patients were then grouped into binary (with or without history) categories for each comorbidity assessed.

Statistical Analysis
All data will be analyzed using GraphPad Prism Software (San Diego, CA). Unpaired, non-parametric t-tests were conducted to determine the significance of patterns among variables.

Summary & Conclusion

1. Statistically significant plasma inflammatory and metabolic biomarker concentration disturbances were observed in ESRD patients on hemodialysis that are specific to a patients prior vascular comorbid conditions.
2. Plasma IL-1a elevation was observed in ESRD patients with history of Stroke or CAD, which further demonstrates the biomarker's known involvement in a number of pathways involving a pro-inflammatory state.
3. Plasma Leptin variations were found in both the Stroke and CHF cohorts. Decreased Leptin was seen in CHF patients, which corroborates recent prospective study evidence that a decreased Leptin in ESRD patients on HD is an independent risk factor of increased all-cause mortality. Conversely, an increased Leptin was seen in Stroke patients.
4. Prior studies have demonstrated that ESRD patients have elevated plasma Resistin levels compared to normal. Despite this known disturbance, ESRD patients with history of stroke were found to have significantly elevated Resistin when compared to those without. This may indicate the biomarker's important role in this disease process.

Clinical Significance

Plasma metabolic and inflammatory biochip profiling of ESRD patients demonstrates the presence of diverse systemic processes that may provide clues into the pathogenesis of such diseases and exposure potential therapeutic targets. Similar profiling of ESRD patients may yield a future prognostic or therapeutic tool for optimal management of these complex patients.

Acknowledgements

The authors gratefully acknowledge the assistance of the dialysis center staff at the Loyola University Medical Center for the facilitation of the collection of the blood samples from patients with ESRD. We are also thankful to the staff of hemostasis and thrombosis research laboratories for their skillful assistance in generating some of the information included in this manuscript. The authors have no conflict of interest for this study.