Up-Regulation of Inflammatory Mediators and Markers of Metabolic Deraignment in End Stage Renal Disease as Studied by Biochip Array Analysis

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

Abstract

Introduction:
End stage renal disease represents a complex syndrome with multiple pathophysiological processes involving vascular, inflammatory, thrombotic, and metabolic deraignment. This study was designed to utilize biochip array technology to compare the inflammatory and metabolic syndrome biomarker profiles of a maintenance hemodialysis cohort (n=81) with healthy normal male and female volunteers (n=41).

Materials and Methods:
The ESRD group represented patients who are under maintenance hemodialysis at the Loyola University Clinic (n=81) and a group of healthy normal individuals (n=50). High sensitivity inflammatory cytokine chips to profile IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-gamma, IL1-alpha, IL1-beta, MCP1, and EGF and metabolic array chip to analyze C-Peptide, ferritin, resistin, insulin, leptin, and PAI-1 were used employing Evidence Investigator (Randox, UK).

Results:
In the inflammatory biochip array analysis, except for IL-2 and EGF, all the inflammatory biomarkers were found to be significantly higher than the normal group ($p<0.0001$). The ESRD group exhibited marked variations in the circulating levels of the inflammatory mediators and the extent of increase also varied. In the metabolic chip array analysis, all of the markers of metabolic deraignment were significantly increased ($p=<0.001$), except insulin, where a trend towards increased levels was noted.

Conclusions:
These results clearly demonstrate the complexity of the pathophysiologic event in ESRD patients. A widespread increase in the inflammatory mediators, coupled with the higher levels of metabolic deraignment markers suggest that the ESRD patients not only have an ongoing inflammatory process but also sustain metabolic deraignment. Profiling of these mediators not only provides an understanding of the pathogenesis of this condition, but may be helpful in the risk stratification and clinical management of these patients.

Introduction

CKD not only puts patients at risk for renal failure, but also for co-morbidities such as cardiovascular disease (CVD) and stroke, and increases all-cause mortality. As MetS and CKD share many of the same risk factors and similar inflammatory pathogenesis, multiple studies have suggested a correlation between CKD and MetS. The purpose of this study is to investigate the prevalence of MetS in ESRD patients. Furthermore, through increasing our understanding of the pathogenesis, disease state, and biomarker profiles of patients with ESRD, we may be able to predict the development of comorbidities, treat aggressively, and offer patients with ESRD a better chance of survival.

Chronic Kidney Disease
Chronic Kidney disease (CKD) is characterized by decreased renal function. It can result from a number of conditions, primarily Diabetes Mellitus, hypertension and glomerulonephritis. These conditions lead to inflammation, oxidative stress, dyslipidemia, and ultimately chronic kidney damage. As the disease progresses, patients may exhibit metabolic acidosis, anemia, mineral metabolism disorders, volume overload and hypertension. Eventually, CKD may advance to ESRD, at which point patients exhibit uremia due to accumulation of toxins that are insufficiently filtered by the kidney, and require hemodialysis or a kidney transplant.

As mentioned above, CKD not only puts patients at risk for renal failure, but also for co-morbidities such as cardiovascular disease (CVD) and stroke, and increases all-cause mortality. The chronic inflammatory state and metabolic waste buildup that accompany ESRD are thought to contribute to atherosclerosis pathogenesis, and can ultimately lead to CVD, deep vein thrombosis (DVT), pulmonary embolism (PE), peripheral vascular disease (PVD), stroke and death.

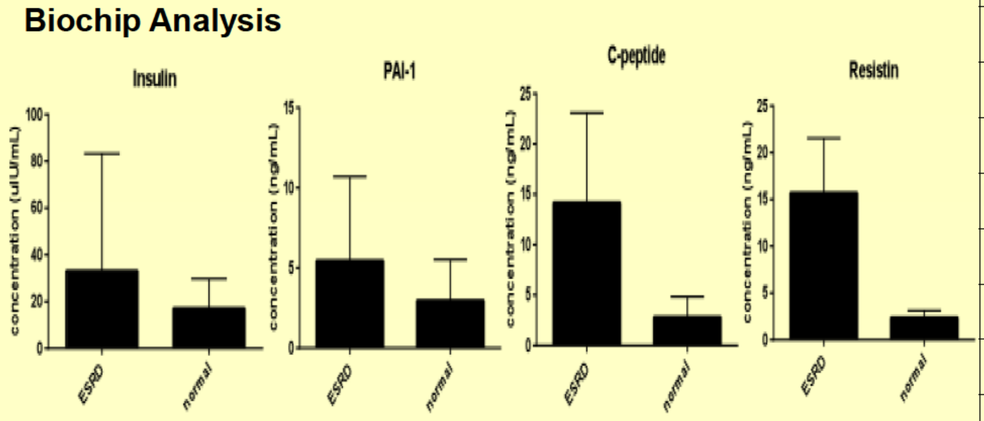
Materials & Methods

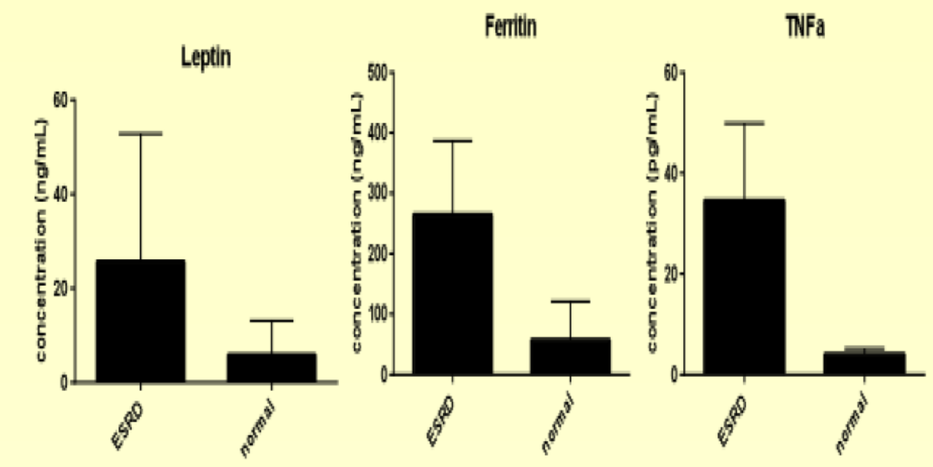
Biomarker evaluation
Under IRB approval, plasma samples collected from 89 patients with ESRD prior to hemodialysis on November 1st and 2nd, 2013. Normal human plasma samples (female & male, 18-35 years old) were purchased from George King Biomedical Inc. (Overland Park, KS). Samples were stored at -80° C. Metabolic and inflammatory cytokine biochips were purchased from RANDOX (Co. Antrim, Northern Ireland) to test C peptide, ferritin, resistin, insulin, TNFα, leptin, PAI-1, IFNg, MCP1, EGF, IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-8, and IL-10. These biomarkers were tested on 82 ESRD and 17 normal samples.

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.

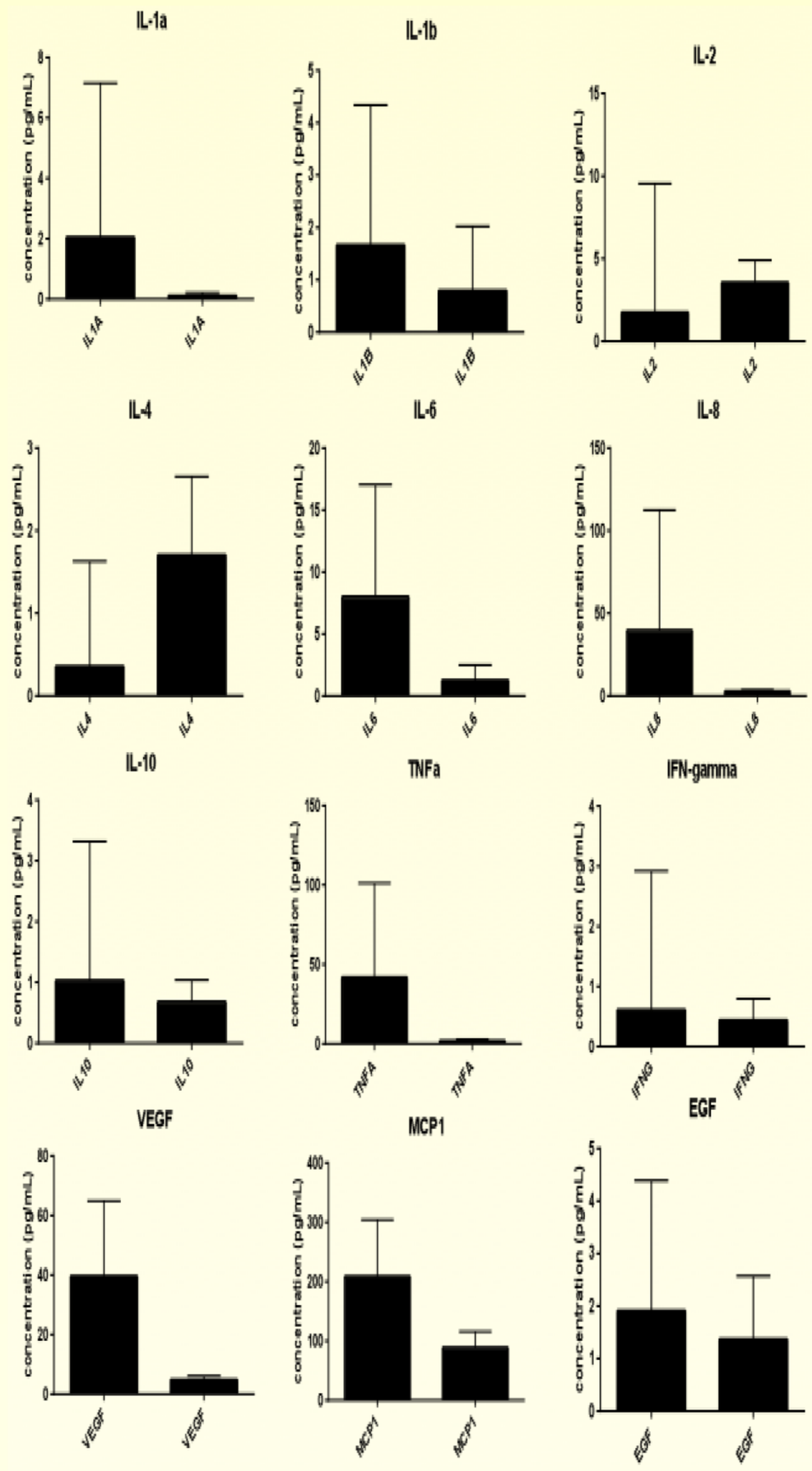
Results

Results of Metabolic Biochip Analysis





Results of Inflammatory Biochip Analysis



Composite Analyzed Data on ESRD vs. normal Populations

	P-value	% difference
C-peptide	<0.0001	120
Resistin	<0.0001	140
Ferritin	<0.0001	133
Insulin	0.4	79
Leptin	0.01	130
PAI-1	0.05	69
IL-2	<0.0001	149
IL-4	<0.0001	42
IL-6	<0.0001	115
IL-8	<0.0001	133
IL-10	0.8989	66
VEGF	<0.0001	150
TNFα	<0.0001	158
IFN-γ	<0.0001	156
IL-1α	<0.0001	118
IL-1β	0.0113	22
MCP1	<0.0001	71
EGF	0.7458	52

Summary

In the inflammatory biochip array analysis, except for IL-2 and EGF, all the inflammatory biomarkers were found to be significantly higher than the normal group ($p<0.0001$). The ESRD group exhibited marked variations in the circulating levels of the inflammatory mediators and the extent of increase also varied. In the metabolic chip array analysis, all of the markers of metabolic deraignment were significantly increased ($p=<0.001$), except insulin, where a trend towards increased levels was noted.

Conclusion

These results clearly demonstrate the complexity of the pathophysiologic event in ESRD patients. A widespread increase in the inflammatory mediators, coupled with the higher levels of metabolic deraignment markers suggest that the ESRD patients not only have an ongoing inflammatory process but also sustain metabolic deraignment. Profiling of these mediators not only provides an understanding of the pathogenesis of this condition, but may be helpful in the risk stratification and clinical management of these patients.

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