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Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease

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Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease.

Background. The prevalence of increased oxidative stress and acute-phase inflammation in patients with chronic kidney disease (CKD) has not been thoroughly investigated.

Methods. Biomarkers of oxidative stress and acute-phase inflammation were measured in a cohort of 60 patients with stage 3–5 CKD compared to a healthy subject cohort. Levels of oxidative stress and inflammation were also compared to estimated glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) formula.

Results. All biomarkers of oxidative stress (plasma protein carbonyl group content, plasma free F_2-isoprostane content, plasma protein reduced thiol content) and all markers of inflammation [C-reactive protein (CRP), interleukin-6 (IL-6)] differed significantly between CKD patients and healthy subjects. There was no significant relationship between estimated GFR and any oxidative stress or inflammation biomarker. CRP levels were higher in patients with known coronary vascular disease (CVD) and in patients not taking angiotensin II inhibitors. Plasma IL-6 levels were significantly higher in patients with known coronary vascular disease and lower in patients taking statins. Biomarkers of oxidative stress were significantly higher in patients with diabetes and hypercholesterolemia.

Conclusion. There is evidence of increased oxidative stress and acute-phase inflammation in patients with stage 3–5 chronic kidney disease compared to healthy subjects that does not closely correlate with estimates of GFR. Among CKD patients, inflammatory biomarkers correlate with known CVD and inversely correlate with the use of angiotensin II inhibitors and statins. A further increase in oxidative stress was noted in diabetic and hypercholesterolemic patients. Inflammation and oxidative stress may contribute to cardiovascular risk in CKD patients.

Data are emerging to suggest there is a higher prevalence of chronic kidney disease (CKD) in the adult United States population than previously appreciated [1], and that a large number of patients at earlier stages of CKD have gone undiagnosed and undertreated [2–4]. For example, data from the Third National Health and Nutrition Examination Survey (NHANES III) suggest that the prevalence of CKD in the United States adult population may be as high as 11%, constituting 19.2 million individuals [1]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) has recently defined the stage of CKD based on the level of glomerular filtration rate (GFR). According to this classification, Stage 3 CKD (moderately decreased GFR) is defined by a GFR of 30–59 mL/min/1.73 m^2, Stage 4 CKD (severely decreased GFR) by a GFR of 15–29 mL/min/1.73 m^2, and Stage 5 CKD (kidney failure) by a GFR <15 mL/min/1.73 m^2 [5]. The NHANES III data also suggest that there are more than 8 million United States adults with an estimated GFR less than 60 mL/min/1.73 m^2, constituting Stage 3–5 chronic kidney disease according to K/DOQI guidelines.

Patients with Stage 3–5 CKD are at risk for progression of kidney disease and development of end-stage renal disease (ESRD). Moreover, these patients appear to be at even greater risk for the development of cardiovascular disease and associated morbidity and mortality. Thus, most patients with Stage 3–5 CKD will die of cardiovascular complications prior to developing ESRD [6]. Several studies in high-risk populations and community-based studies have identified the level of kidney dysfunction as an independent risk factor for cardiovascular outcomes and all-cause mortality [7–13]. Currently, available data concerning cardiovascular risk factors in CKD patients are largely derived from retrospective analyses with limited biochemical analysis available of potential uremia-related cardiovascular risk factors.

In ESRD patients, it is now well-established that there is a high prevalence of acute-phase inflammation and oxidative stress, both of which are associated with the high rate of cardiovascular morbidity and mortality [14–17]. Whether inflammation and oxidative stress are

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independent "uremia" associated cardiovascular risk factors that also apply to the CKD population is unclear. Currently, there are few prevalence studies examining biomarkers of oxidative stress and inflammation in the larger population of patients with CKD. Given the high prevalence of cardiovascular disease in the CKD population, we hypothesized that this population would manifest an increase in biomarkers of inflammation and oxidative stress, and that these biomarkers would inversely correlate with GFR. We therefore examined commonly utilized biomarkers of acute-phase inflammation and oxidative stress status in a cohort of patients with stage 3–5 CKD not receiving renal replacement therapy.

METHODS

Patient characteristics

The study subject population consisted of 60 consecutive patients followed at a CKD clinic who gave informed consent to participate in a cross-sectional study. The study protocol was approved by the Maine Medical Center IRB. Twenty-two of 60 patients were female (37%), and the mean age was 67 ± 14 (range 32–91). GFR was estimated using the MDRD prediction equation in mL/min/1.73 m^2 [170 × (creatinine)$^{-0.999}$ × (age)$^{-0.76}$ × (urea)$^{-0.170}$ × (albumin)$^{+0.318\times}$ 0.762 if female] [18]. The range of estimated GFR was from 7 to 54 mL/min (mean 27 mL/min, SD ± 11). Study subjects underwent a detailed review of their medical history, and laboratory measurements consisting of biomarkers of oxidative stress status and acute-phase inflammation at the time of study enrollment. Etiology of chronic kidney disease was determined by chart review. The etiologies consisted of hypertensive nephrosclerosis (24 patients), diabetic glomerulosclerosis (19 patients), glomerulonephritis (4 patients), polycystic kidney disease (2 patients), renovascular disease (4 patients), scleroderma (1 patient), reflux nephropathy (1 patient), renal dysplasia (1 patient), sarcoidosis (1 patient), atheroembolic disease (1 patient), obstructive uropathy (1 patient), and loss of renal mass from malignancy (1 patient). Prevalent coronary vascular disease was defined by history of a revascularization procedure (e.g., either a percutaneous coronary intervention or coronary artery bypass grafting). Hypercholesterolemia was defined by charted diagnosis and/or the use of statins or other anti-hypercholesterolemic medications. A healthy subject pool was utilized for comparison of biomarkers of oxidative stress status and inflammation [$N = 54$ for C-reactive protein (CRP), $N = 50$ for interleukin-6 (IL-6), $N = 70$ for thiols, $N = 53$ for carbonyls, and $N = 48$ for F_2-isosprostanes]. Healthy subjects were obtained from health care facility employees and a local geriatric primary care practice. The mean age of healthy subjects was 51.4 ± 1.7 years (range 22–93), which was larger than the CKD population ($P < 0.001$). Fifty-eight percent were female and 95% were Caucasian. Informed consent was obtained prior to phlebotomy.

Blood sampling

For CRP measurements, blood was drawn into Vacutainer® (Becton-Dickinson, Franklin Lakes, NJ, USA) serum separator tubes containing clot activator. Tubes were kept at room temperature and centrifuged within one hour of blood draw. For IL-6 and oxidative stress biomarker measurements, blood was drawn into Vacutainer® tubes containing EDTA. Tubes were immediately placed on ice, centrifuged, and kept at 4°C until frozen. Plasma and serum samples were stored at −70°C until analysis.

Plasma protein reduced thiol content

The assay for plasma protein reduced thiol content measures the major source of reducing equivalents (or antioxidant capacity) available in the plasma. Thiol groups were assayed according to the method of Ellman [19] as modified by Hu [20], as we have previously described [21]. Briefly, 1 mL of buffer containing 0.1mol/L Tris, 1 mmol/L EDTA, pH 8.2, and 50 μL plasma was added to cuvettes, followed by 50 μL 10 mmol/L 5′5′dithio-bis (2-nitrobenzoic acid) (DTNB) in methanol. Blanks were run for each sample, prepared as above, with the exception that there was no DTNB in the methanol. Following incubation for 15 minutes at room temperature, sample absorbance was read at 412 nm on a Lambda2 spectrophotometer (Perkin Elmer, Norwalk, CT, USA). Sample and reagent blanks are subtracted. The concentration of thiol groups was determined using the 5-thio-2-nitrobenzoic acid (TNB) molar extinction coefficient of 14,100 mol/L^{-1} cm^{-1}, and results are reported as micromoles per liter.

Plasma protein carbonyl group content

Plasma protein carbonyl content measures reactive aldehyde content as an index of oxidative stress. Carbonyl groups are measured using the Zentech PC Test Kit from Zenith Technology (Dunedin, New Zealand). This kit follows the method outlined by Buss et al [22], as amended by Winterbourn and Buss [23], which utilizes derivatization of protein carbonyls in samples and oxidized protein standards with dinitrophenylhydrazine (DNPH), followed by enzyme-linked immunosorbent assay (ELISA) with anti-DNP antibody as we have previously described [21]. Standard ELISA techniques for labeling and visualizing labeled molecules were used. Absorbance was read at 450 nm on an MRX microplate reader from Dynex Technologies (Chantilly, VA, USA). A standard curve was plotted and the carbonyl concentration of samples was read off the curve.

Table 1. Comparison of inflammatory and oxidative stress biomarkers in CKD patients and healthy subjects

	Healthy subjects	CKD patients	*P* value
CRP *mg/L*	1.8 (0–28.6)	3.9 (0.6–28.4)	0.02
IL-6 *pg/mL*	2.1 (1.5–12.5)	6.4 (1.5–95.4)	0.001
Thiols μ*mol/L*	415 (262–497)	303 (193–435)	<0.001
Carbonyls *nmol/mg protein*	0.029 (0–0.154)	0.061 (0.020–0.134)	<0.001
F_2-isoprostanes *ng/mL*	0.036 (0.019–0.179)	0.046 (0.025–0.156)	<0.001

Abbreviations are: CRP, C-reactive protein; IL-6, interleukin-6; CKD, chronic kidney disease. Data are given as medians, with range in parentheses.

Plasma-free F_2-isoprostane content

F_2-isoprostanes are lipid peroxidation products produced by free radical mediated non-enzymatic oxidation of arachidonic acid. Free F_2-isoprostanes esterified to plasma lipids were quantified in plasma by gas chromatography/negative-ion chemical ionization mass spectrometry as we have described [24]. The precision of the assay for free F_2-isoprostanes was ± 6%, and the accuracy was 96%. Data are expressed in ng/mL.

Inflammatory biomarkers

Plasma IL-6 cytokine concentrations were determined by ELISA with kits from BioSource International (Camarillo, CA, USA). Detection limit of the assay was 1.5 pg/mL. High sensitivity CRP was measured in serum using nepholometry.

Statistics

Descriptive results are reported as medians and ranges. Distribution of variables of interest were examined and tested for normality using Shapiro-Wilk statistic. Because these distributions departed significantly from normality, nonparametric tests were used for bivariate comparisons, including tests of differences in medians and Spearman's correlations. For comparisons of CKD patients and healthy subjects and CKD patients by cardiovascular risk factor status, data were analyzed using the Mann-Whitney *U* test. Within the CKD population, Spearman correlation coefficients were used to assess relationships among GFR, markers of nutritional status, biomarkers of inflammation, and oxidative stress status. Multiple linear regression was used to examine the relationship of cardiovascular risk factors and CRP; because CRP was skewed, the dependent variable was log transformed.

RESULTS

Biomarkers of inflammation and oxidative stress status are increased in CKD patients compared to healthy subjects

Table 1 demonstrates that levels of the inflammatory markers CRP ($P = 0.02$) and IL-6 ($P = 0.001$) were significantly higher in CKD patients compared to healthy subjects. Similarly, the plasma levels of protein-associated carbonyl content ($P < 0.001$) and free F_2-isoprostane content ($P = 0.001$) are significantly higher in CKD patients compared to healthy subjects. Plasma protein–reduced thiol content was significantly lower in CKD patients compared to healthy subjects ($P < 0.001$).

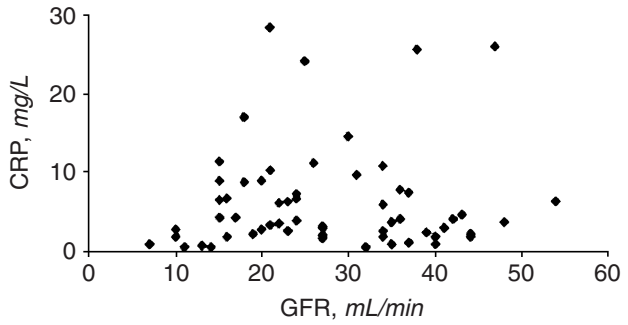

Fig. 1. The relationship between estimated glomerular filtration rate and C-reactive protein. The coefficient of correlation is $R = 0.03$, $P = 0.84$.

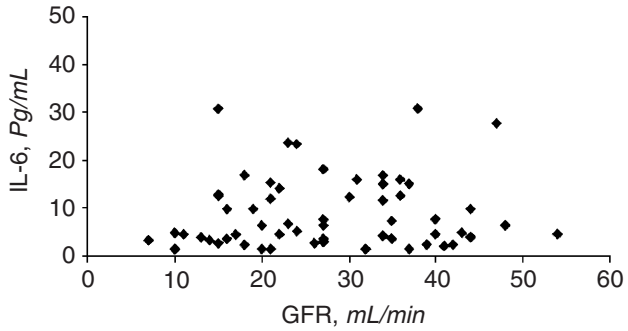

Fig. 2. The relationship between estimated glomerular filtration rate and plasma interleukin-6 level. The coefficient of correlation is $R = 0.08$, $P = 0.54$.

Relationship of GFR to biomarkers of inflammation and oxidative stress status in CKD patients

To examine the potential relationship between decrement in GFR and acute-phase inflammation, the level of GFR was compared to CRP and IL-6 levels in CKD patients. Figures 1 and 2 demonstrate that there are no significant correlations between GFR and levels of CRP ($R = 0.03$, $P = 0.84$) or IL-6 ($R = 0.08$, $P = 0.54$). Similarly, Figures 3, 4, and 5 demonstrate that there was no significant correlation between GFR and the level of plasma protein carbonyl content ($R = 0.08$, $P = 0.56$), plasma F_2-isoprostane content ($R = 0.02$, $P = 0.89$), or plasma protein–associated free thiol content ($R = -0.14$, $P = 0.28$). If patients receiving angiotensin- converting enzyme inhibitors or angiotensin receptor blockers were excluded from the analysis, there was still no significant correlation between any biomarker of oxidative stress or inflammation and GFR ($R = 0.16$ and $P = 0.68$ for CRP, other data not shown).

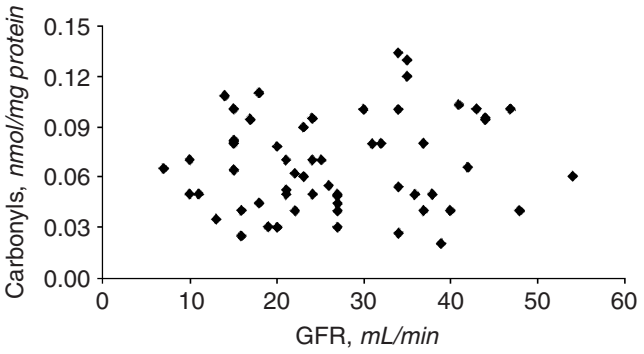

Fig. 3. The relationship between estimated glomerular filtration rate and plasma protein carbonyl content. The coefficient of correlation is $R = 0.08$, $P = 0.56$.

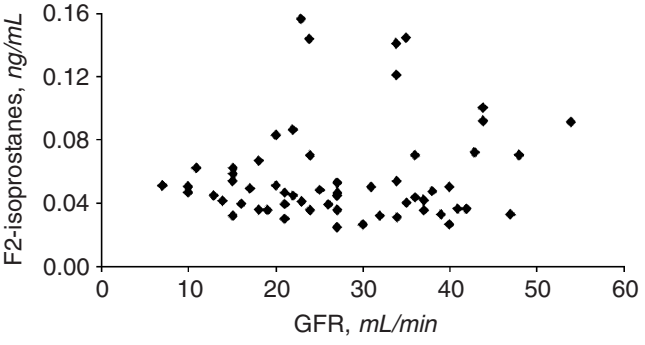

Fig. 4. The relationship between estimated glomerular filtration rate and plasma free F_2-isoprostane content. The coefficient of correlation is $R = 0.02$, $P = 0.89$.

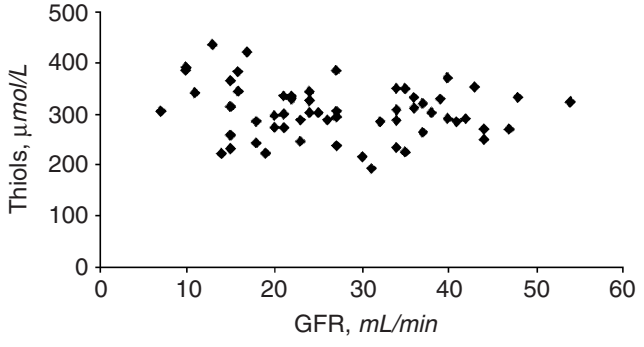

Fig. 5. The relationship between estimated glomerular filtration rate and plasma protein reduced thiol content. The coefficient of correlation is $R = 0.14$, $P = 0.28$.

Association of cardiovascular risk factors with inflammation and oxidative stress

Relationships between traditional cardiovascular risk factors, cardiovascular therapeutics, and biomarkers of inflammation and oxidative stress in this CKD cohort are presented in Table 2. Levels of CRP correlate with age (data not shown) and are significantly higher in patients with known coronary vascular disease compared to the remainder of CKD patients ($P < 0.001$). Of interest, levels of CRP are significantly lower in patients for whom angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are prescribed compared to patients not receiving these types of medication ($P < 0.05$). Patients receiving statins also had significantly lower IL-6 levels ($P < 0.05$). The use of angiotensin inhibitors was similar in patients with Stage 3 CKD (12/25, 48%) and with Stage 4–5 CKD (12/35, 34%). Similarly, statin use was similar in patients with Stage 3 CKD (14/25, 56%) to patients with Stage 4–5 CKD (15/35, 43%). All plasma biomarkers of oxidative stress status did not differ significantly between patients with or without known coronary vascular disease or between patients receiving or not receiving angiotensin II inhibitors.

Given the novelty of the finding that the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were associated with lower CRP levels, a multivariable regression analysis was conducted including age, gender, diabetes mellitus, angiotensin II inhibitor use, coronary artery disease, hypercholesterolemia, and smoking. Additional models were constructed, controlling for GFR. In all models, the use of ACE inhibitors or angiotensin receptor blockers was significantly negatively associated with CRP (Table 3).

Diabetes mellitus and hypercholesterolemia are considered "traditional" risk factors for cardiovascular disease. In this patient cohort, hypercholesterolemic patients exhibited an increase in biomarkers of oxidative stress status, with significantly increased F_2-isoprostane content ($P < 0.05$), and lower plasma protein reduced thiol content ($P < 0.05$) compared to patients without a diagnosis of hypercholesterolemia. A trend toward a difference in F_2-isoprostane content was also observed in patients on statins (who constitute a subset of hypercholesterolemic patients in this study) compared to patients not receiving statins, which did not reach significance. Patients with diabetes mellitus have significantly higher plasma protein carbonyl content ($P < 0.05$) and a trend toward lower plasma protein reduced thiol content ($P = 0.07$) compared to CKD patients without diabetes mellitus, demonstrating a further increase in oxidative stress in diabetic patients.

DISCUSSION

In this study, we have examined commonly utilized biomarkers of inflammation and oxidative stress status to examine a cohort of patients with stage 3–5 CKD not receiving renal replacement therapy. Our hypothesis was that these markers would negatively correlate with the level of GFR and become more prominent at the very late stages of CKD. In contrast to our original hypothesis, our results demonstrate that increased oxidative stress and inflammation are prevalent in patients with CKD well before the initiation of renal replacement therapy, but not

Table 2. Association of cardiovascular risk factors with inflammation and oxidative stress biomarkers

	IL-6 *pg/mL*	CRP *mg/L*	Thiols μmol/L	Carbonyls *nmol/mgprotein*	F_2 Lsoprostanes *ng/mL*
Diabetes mellitus					
No ($N = 31$)	6.9 (1.5–95.4)	4.1 (0.3–28.4)	319 (221–435)	0.052 (0.020–0.110)	0.046 (0.030–0.156)
Yes ($N = 29$)	4.9 (1.5–30.5)	3.7 (0.6–25.9)	290 (193–386)	0.080 (0.027–0.134)[a]	0.047 (0.025–0.145)
Tobacco use					
No ($N = 55$)	6.3 (1.5–95.4)	3.7 (0.6–28.4)	301 (193–435)	0.064 (0.020–0.134)	0.046 (0.025–0.156)
Yes ($N = 5$)	15.5 (4.5–30.5)	4.3 (3.3–6.7)	323 (232–334)	0.052 (0.050–0.080)	0.062 (0.039–0.144)
Known CVD					
No ($N = 41$)	5.1 (1.5–30.5)	3.1 (0.6–11.3)	306 (223–435)	0.060 (0.020–0.134)	0.046 (0.025–0.156)
Yes ($N = 19$)	11.8 (1.5–95.4)[a]	8.7 (0.6–28.4)[b]	298 (193–385)	0.064 (0.030–0.110)	0.046 (0.026–0.072)
Hypercholesterolemia					
No ($N = 16$)	6.7 (1.5–23.3)	3.1 (0.6–28.4)	330 (221–435)	0.051 (0.020–0.095)	0.042 (0.026–0.070)
Yes ($N = 44$)	5.0 (1.5–95.4)	4.5 (0.6–25.9)	300 (193–386)	0.063 (0.025–0.134)	0.050 (0.025–0.156)[a]
ACE inhibitor use					
No ($N = 36$)	6.4 (1.5–30.5)	6.2 (0.6–28.4)	319 (193–421)	0.058 (0.020–0.110)	0.046 (0.026–0.156)
Yes ($N = 24$)	5.5 (1.5–95.4)	2.2 (0.6–24.1)[a]	291 (223–435)	0.074 (0.027–0.134)	0.051 (0.025–0.145)
Statin use					
No ($N = 31$)	9.8 (1.5–95.4)	4.2 (0.6–28.4)	301 (193–435)	0.064 (0.020–0.110)	0.042 (0.026–0.156)
Yes ($N = 29$)	4.5 (1.5–27.5)[a]	3.1 (0.6–25.9)	305 (223–386)	0.060 (0.027–0.134)	0.051 (0.025–0.145)

[a] $P < 0.05$
[b] $P < 0.001$

Table 3. Multivaviate regression analysis of angiotensin inhibitors and C- reactive protein levels

	Coefficient	Standard error	*P*
ACE alone	−0.84	0.23	0.0006
ACE + demographics[a]	−0.71	0.21	0.001
ACE + demographics + cardiac risk factors[b]	−0.60	0.24	0.01
ACE + demographics + cardiac risk factors + GFR	−0.75	0.23	0.002

ACE is angiotensin-converting enzyme.
[a]Demographics, age, gender.
[b]Cardiac risk factors, known CAD, diabetes, hypercholesterolemia, smoking.

closely correlated with estimates of GFR. In addition, we observed a positive correlation between the inflammatory biomarkers CRP and IL-6 and the presence of known cardiovascular disease and a negative correlation with angiotensin inhibitor and statin use.

The most notable finding in this study is that there does not appear to be a close relationship between GFR and the extent to which increased inflammation and oxidative stress are present in CKD patients. This is in contradistinction to many "classical" uremic toxins, where there is a close inverse relationship between plasma concentration of the toxin and the GFR [25]. A potential explanation for the limited correlation of biomarkers of oxidative stress and inflammation with GFR may be that many of the solutes used as biomarkers undergo renal clearance primarily via renal tubular metabolism rather than glomerular filtration. For example, aldehyde-modified proteins (as detected in the carbonyl assay) likely undergo metabolism via aldehyde dehydrogenase, an enzyme associated with tubular epithelial cells [26, 27]. Similarly, the redox status of amino acid–containing low-molecular-weight thiols are extensively and selectively modified by proximal tubular metabolism and transport [28–30]. Thus, plasma protein thiol oxidation and plasma protein carbonyl content may be largely regulated by proximal tubular function and not glomerular filtration.

Inflammation is a common feature of ESRD; however, there have been few studies examining biomarkers of acute-phase inflammation in patients with less advanced kidney disease. Furthermore, the extent to which GFR is related to biomarkers of inflammation is controversial. Several studies have associated changes in GFR with biomarkers of inflammation, particularly in patients with advanced disease [31–34]. In baseline data from the Cardiovascular Health Study, levels of CRP and IL-6 were found to be significantly higher in patients with renal insufficiency compared to patients with normal kidney function [35]. In a recent community-based cross-sectional study, increased CRP was found to associate with decreased GFR. However, in a recent study utilizing the Modification of Diet in Renal Disease (MDRD) baseline data, serum CRP levels were found not to correlate with either GFR or disease progression [36]. The findings in the present study would support these data that elevations in biomarkers of inflammation such as CRP and IL-6 are present earlier in the course of kidney disease than previously recognized, but would suggest they are not necessarily well correlated with GFR.

Oxidatively modified amino acids and plasma proteins can serve as important in vivo biomarkers of oxidative stress [37]. In this study we examined plasma protein thiol group oxidation and carbonyl content as in vivo biomarkers of oxidative stress. The protein carbonyl assay measures reactive aldehydes formed as end products of a variety of oxidative reactions. The potential significance of elevated aldehyde concentrations is clearly demonstrated by their prominent role in the pathogenesis of atherosclerosis [38, 39]. Reduced extracellular

thiols measured in this study as plasma protein reduced thiol content are an important component in antioxidant defense with high relevance to cardiovascular disease. In an earlier study, we demonstrated a similar increase in plasma protein carbonyl content and decreased plasma protein reduced thiol content in a small cohort of patients with advanced CKD compared to healthy subjects [21]. The present study extends these findings in a larger cohort by demonstrating increased plasma protein oxidation is a nearly universal finding in patients with stage 3–5 CKD, without being closely related to estimated GFR. In this study we also examined plasma F_2-isoprostane content as a lipid biomarker of oxidative stress, and demonstrated elevated levels in CKD patients compared to healthy subjects. Measurement of F_2-isoprostanes are considered a reliable indicator of lipid peroxidation and have previously been demonstrated by our group and others to be elevated in maintenance hemodialysis patients [40, 41].

Although increased oxidative stress is increasingly recognized as an important metabolic accompaniment to ESRD, there have been remarkably few studies utilizing biomarkers of oxidative stress in the CKD population. Annuk et al reported on 37 patients with a mean creatinine clearance of 25 mL/min and demonstrated alterations in lipid peroxidation end products and glutathione content in patients with CKD. Of note, these investigators correlated alterations in oxidative stress status with endothelial dysfunction in the CKD patient cohort [42]. Bolton et al examined 17 patients with chronic kidney disease (GFR <50 mL/min) and demonstrated increased autoantibodies to oxidized low-density lipoprotein (LDL) [43]. Mezzano et al examined 64 patients with advanced CKD and demonstrated increases in lipid peroxidation and advanced oxidation protein products (AOPP) [44]. Witko-Sarsat et al examined a cohort of 162 uremic patients, demonstrating elevations in AOPP and a close relationship of AOPP accumulation to GFR [45]. These studies suggest that the myriad of oxidative stress changes associated with ESRD are also prevalent in the CKD population.

An interesting finding in this study is that patients with CKD being treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers appear to have lower CRP levels than patients not receiving these therapeutic agents. The renin-angiotensin system is an important regulator of blood pressure and fluid and electrolyte homeostasis and plays a central role in the progression of glomerulosclerosis, nephrosclerosis, and renal interstitial fibrosis. As a consequence, angiotensin II inhibitors are frequently used in an attempt to arrest the progression of renal disease and to reduce proteinuria. Many of the effects of angiotensin II signaling on target tissues are mediated via increased production of reactive oxygen species through activation of the NAD(P)H oxidases [46, 47]. Several recent studies have also demonstrated that the use of angiotensin II inhibitors may have potent anti-inflammatory effects [48–50]. A single previous study of patients with advanced CKD noted that patients receiving ACE inhibitors or angiotensin receptor blockers (ARBs) had lower plasma tumor necrosis factor alpha levels and better nutritional status relative to patients not treated with ACE inhibitors [51]. This study suggests that the beneficial effects of angiotensin inhibition may operate through anti-inflammatory mechanisms in the CKD population. The finding of an association between ACE inhibitors and/or ARBs and lower CRP levels in the present observational study cannot be utilized to make causal inferences, and should be interpreted with caution, given the cross-sectional study design and relatively small sample size. This potential relationship should be examined prospectively in controlled studies. Of note, a significant relationship between statin use and CRP levels was not identified in this study (even though the relationship between statin use and IL-6 levels was significant), despite previous studies in other patient populations that have observed such a relationship. However, a significant association may have been missed due to sample size in the present study, as the magnitude of previously observed effects of statins on CRP have been relatively small (approximately 15%) [52–54]. Similarly, an association between the levels of oxidant stress biomarkers and cardiovascular disease may have been missed due to sample size. A weakness in the present study is its cross-sectional, observational nature, as well as the relatively small sample size. In an observational study, it is possible to demonstrate associations between CKD and the presence of increased oxidative stress and inflammation, but not to determine causal relationships. Additionally, because of the relatively small sample size, there may be relationships between clinical parameters (such as etiology of renal disease, gender, race, age, nutritional status, and conventional cardiovascular risk factors), inflammation, and oxidative stress in the CKD population that were not determined due to type B statistical errors.

CONCLUSION

The present study is useful in its clear-cut demonstration of excess inflammation and oxidative stress in the CKD cohort and in the lack of a demonstrated strong correlation with the degree of GFR. This provides hypothesis-driven support for prospective longitudinal observational and randomized clinical trials examining oxidative stress and inflammation in the CKD population, as well as potential cardiovascular consequences.

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