View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

facilitate CKD recognition across the broad landscape of the health-care system and to promote the provision of CKD-specific safe care are lacking and should be developed. Nevertheless, the findings of Hug *et al.*,[6] and their endorsement of the use of CPOE systems, are important steps toward increasing the medical community's awareness of the sensitivity of patients with CKD to medication administration and toward improving the safety of their care. As nephrologists, we should expand beyond our traditional 'nephrocentric' view of the universe. Efforts to prevent nephrotoxicity or to slow progression of CKD should not be abandoned, but a more holistic approach to enhancing patient safety should become a priority of our collective practice.

DISCLOSURE

The authors declared no competing interests.

REFERENCES

1. Fink JC, Brown J, Hsu VD *et al.* Is chronic kidney disease a threat to patient safety? *Am J Kidney Dis* 2009; **53**: 681–688.
2. Stevens LA, Fares G, Fleming J *et al.* Low rates of testing and diagnostic codes usage in a commercial clinical laboratory: evidence for lack of physician awareness of chronic kidney disease. *J Am Soc Nephrol* 2005; **16**: 2439–2448.
3. Aronoff GR, Berms JS, Brier ME *et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*, 5th edn. American College of Physicians: Philadelphia, 2007, pp 1–165 .
4. Corsonello A, Pedone C, Corica F *et al.* Concealed renal insufficiency and adverse drug reactions in elderly hospitalized patients. *Arch Intern Med* 2005; **165**: 790–795.
5. Blix HS, Viktil KK, Moger TA *et al.* Use of renal risk drugs in hospitalized patients with impaired renal function: an underestimated problem? *Nephrol Dial Transplant* 2006; **21**: 3164–3171.
6. Hug BL, Witkowski DJ, Sox CM *et al.* Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney. *Kidney Int* 2009; **76**: 1192–1198.
7. Chertow GM, Lee J, Kuperman GJ *et al.* Guided medication dosing for inpatients with renal insufficiency. *JAMA* 2001; **286**: 2839–2844.
8. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003; **12**: 194–200.
9. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.
10. Kucukarsian SN, Peters M, Mlynarek M *et al.* Pharmacists on rounding teams reduce preventable adverse drug events in hospital general units. *Arch Intern Med* 2003; **163**: 2014–2018.

see original article on page 1148

Advanced oxidation protein products: a causative link between oxidative stress and podocyte depletion

Youhua Liu[1]

Advanced oxidation protein products (AOPPs), a protein biomarker of increased oxidative stress, are elevated in uremic patients. Zhou *et al.* demonstrate that chronic administration of AOPPs induces podocyte apoptosis and proteinuria in normal rats via a cascade of signaling events. This study for the first time establishes a causative link between oxidative stress and podocyte depletion and could have broad implications in our understanding of the pathogenic mechanism of proteinuria.

Kidney International (2009) **76,** 1125–1127. doi:10.1038/ki.2009.352

Increased oxidative stress, resulting from an imbalance between oxidant production and antioxidant reserves, is highly prevalent in a wide variety of chronic kidney diseases (CKD).[1,2] Oxidative, as well as carbonyl, stress in uremic states often incites damage to biologically important macromolecules, including proteins, lipids, carbohydrates, and nucleic acids, and causes them to undergo structural modifications, which leads to generation of the so-called advanced oxidation protein products (AOPPs), advanced lipoxidation end products, and advanced glycation end products. AOPPs are a family of oxidized, dityrosine-containing protein products generated during excessive production of oxidants and often carried by albumin *in vivo*.[3] Accumulation of plasma and renal AOPPs is a common pathologic finding in dialysis patients, as well as in patients with diabetes and metabolic syndrome. Accordingly, the levels of plasma and tissue AOPPs are postulated as a reliable marker to estimate the degree of oxidant-mediated protein damage in uremic patients.

Emerging evidence indicates that AOPPs may not merely be a surrogate marker for oxidative stress in the injured kidney; they are actually a new class of renal pathogenic mediators as well. Clinical studies have shown that AOPP level is a strong predictor for the prognosis of IgA nephropathy.[4] In experimental models, chronic accumulation of plasma AOPPs in rats is associated with an increase in urinary protein excretion, decreased creatinine clearance, exaggerated macrophage infiltration, and aggravated glomerulosclerosis in remnant kidney and diabetic nephropathy.[5] Given that AOPPs are capable of inducing renal expression of proinflammatory cytokines and activate nuclear factor-κB signaling, their detrimental effects are often thought to result from the activation of a redox-sensitive inflammatory pathway. Not surprisingly, AOPPs are also implicated in the pathogenesis of atherosclerosis and cardiovascular disorders in patients with chronic renal insufficiency. In fact, AOPPs have been identified as an independent

[1]*Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA*
Correspondence: *Youhua Liu, Department of Pathology, University of Pittsburgh School of Medicine, S-405 Biomedical Science Tower, 200 Lothrop Street, Pittsburgh, Pennsylvania 15261, USA. E-mail: liuy@upmc.edu*

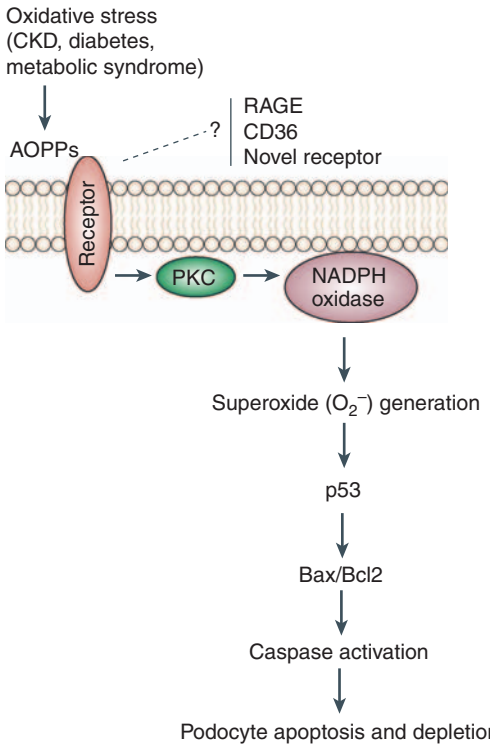

Figure 1 | Oxidative stress leads to podocyte depletion in CKD via AOPPs. Chronic accumulation of AOPPs in CKD, as well as in diabetes mellitus and metabolic syndrome, triggers a cascade of signaling events that lead to protein kinase C/nicotinamide adenine dinucleotide phosphate oxidase activation, superoxide (O_2^-) generation, p53/Bax/caspase activation, and finally podocyte apoptosis and depletion. Whether AOPPs transmit their signals via binding to their own (novel) receptor, or via the receptor for advanced glycation end products (RAGE) and CD36, remains to be determined. AOPPs, advanced oxidation protein products; CKD, chronic kidney disease; NADPH, nicotinamide adenine dinucleotide phosphate; PKC, protein kinase C.

risk factor for atherosclerotic cardiovascular events in CKD.[6] *In vitro* studies reveal that AOPPs induce vascular endothelial and smooth muscle cell dysfunction by activating nuclear factor-κB and p38 mitogen-activated protein kinase signaling[7,8] and therefore could directly contribute to the excessive cardiovascular risk in uremic patients.

Zhou and colleagues[9] (this issue) now report that chronic administration of AOPP-modified albumin by intravenous injections results in intrarenal accumulation and dramatically induces podocyte apoptosis and proteinuria in normal, healthy rats. Consistently, incubation of cultured podocytes with AOPP-modified albumin at a concentration comparable to that in the blood circulation of uremic patients also triggers the death of podocytes *in vitro*. It is particularly interesting that glomerular podocytes appear to be especially vulnerable to AOPP exposure, and podocyte apoptosis occurs at a rate of an average of 3.5 cells per glomerular cross-section at 5 weeks after injection,[9] which is about 17% of the entire glomerular podocyte population in that setting. This magnitude of podocyte apoptosis *in vivo* seems astonishing, as it is approximately 10- to 100-fold more frequent than that reported in most publications of other kidney disease models. Notably, such an effect of AOPPs on podocytes appears not to be related to their particular formulation *in vitro*, because AOPPs isolated from the serum of uremic patients display an almost identical potency in triggering podocytes' apoptotic death.[9] This study unambiguously establishes a causative link between oxidative stress and podocyte apoptosis and depletion, and illustrates that elevated levels of AOPPs play a direct role in the pathogenesis of proteinuria in CKD.

Podocytes and their foot processes are an integral component of the glomerular filtration barrier. Increasing evidence suggests that disruption of podocyte integrity plays an essential role in causing defective glomerular filtration and proteinuria in the majority of genetic and acquired forms of glomerular diseases. In the pathologic setting, podocytes may respond to injurious stimuli in different ways, including hypertrophy, dedifferentiation, epithelial-to-mesenchymal transition, detachment, and apoptosis.[10,11] It remains a mystery what determines the ultimate path a podocyte might choose to take in response to a particular insult. The differential responses of podocytes may not only depend on the severity and/or duration of a specific injury but are also likely determined by the characteristic nature of that insult. In this regard, AOPPs appear to be a particularly potent inducer of podocyte apoptosis both *in vivo* and *in vitro*. Needless to say, podocyte depletion after apoptotic death in the glomeruli would inevitably cause impaired glomerular filtration, leading to the development of proteinuria and glomerulosclerosis.

The mechanism by which AOPPs provoke podocytes to undergo apoptosis is eloquently elucidated by the combined *in vitro* and *in vivo* approach of Zhou *et al.*[9] (Figure 1), which represents one of the many strengths of their study. They found that an elevated level of AOPPs induces intracellular superoxide (O_2^-) generation in podocytes by a mechanism involving nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Intriguingly, AOPPs not only activate NADPH oxidase through a protein kinase C-dependent pathway but also induce the expression of major components of this enzyme complex *in vivo* and *in vitro*, thereby leading to an excessive generation of intracellular superoxide, which in turn provokes the classical p53/Bax/caspase-dependent apoptosis pathway (Figure 1). Hence, AOPPs induce podocyte apoptosis via a cascade of signaling events and ultimately couple oxidative stress to a principal, p53-dependent cell-death machinery.

The present study also raises more new questions. One fundamental issue to be addressed is exactly how AOPPs transmit their signals across the plasma membrane to elicit cellular activities. One can assume that this probably requires a transmembrane receptor for AOPPs. Thus far,

whether there is a dedicated, unique transmembrane receptor for AOPPs remains an open question. Earlier studies have shown that AOPPs are capable of using the receptor for advanced glycation end products (RAGE) for their signaling in vascular endothelial cells.[7] Likewise, AOPPs could use CD36, a class B transmembrane multiligand scavenger receptor that binds to oxidized proteins and is induced in renal tubular epithelial cells in CKD, for transmitting their signals.[12] In this context, it is conceivable that AOPPs may induce podocyte apoptosis by using RAGE or CD36 receptors. As both RAGE and CD36-knockout mice are currently available, one might anticipate a definite answer to this postulation in the near future.

The findings presented by Zhou and colleagues could have broad implications in our understanding of the pathogenesis of podocyte depletion and proteinuria in CKD. As end-stage kidney disease is now recognized to be associated with states of increased oxidative stress, AOPP-mediated podocyte apoptosis would undoubtedly play a critical role in promoting proteinuria and accelerating glomerulosclerosis, although it remains uncertain whether this pathway is active and operated in the early stage of kidney disease. In addition, many pathogenic factors, such as hyperglycemia, angiotensin II, and transforming growth factor-β1, are able to trigger intracellular superoxide generation. Therefore, the signal cascade elucidated in this study might potentially be a convergent pathway leading to podocyte depletion in CKD patients.

Given that inhibition of NADPH oxidase with apocynin effectively protects podocytes from AOPP-mediated apoptosis *in vivo* and *in vitro*, strategies aimed at reducing oxidative stress might prevent podocyte loss, thereby blocking the progression of CKD in the clinical setting.

DISCLOSURE
The author declared no competing interests.

REFERENCES

1. Okamura DM, Himmelfarb J. Tipping the redox balance of oxidative stress in fibrogenic pathways in chronic kidney disease. *Pediatr Nephrol* advance online publication, 7 May 2009, doi:10.1007/s00467-00009-01199-00465.
2. Forbes JM, Coughlan MT, Cooper ME. Oxidative stress as a major culprit in kidney disease in diabetes. *Diabetes* 2008; **57**: 1446–1454.
3. Witko-Sarsat V, Friedlander M, Capeillere-Blandin C *et al.* Advanced oxidation protein products as a novel marker of oxidative stress in uremia. *Kidney Int* 1996; **49**: 1304–1313.
4. Descamps-Latscha B, Witko-Sarsat V, Nguyen-Khoa T *et al.* Early prediction of IgA nephropathy progression: proteinuria and AOPP are strong prognostic markers. *Kidney Int* 2004; **66**: 1606–1612.
5. Li HY, Hou FF, Zhang X *et al.* Advanced oxidation protein products accelerate renal fibrosis in a remnant kidney model. *J Am Soc Nephrol* 2007; **18**: 528–538.
6. Descamps-Latscha B, Witko-Sarsat V, Nguyen-Khoa T *et al.* Advanced oxidation protein products as risk factors for atherosclerotic cardiovascular events in nondiabetic predialysis patients. *Am J Kidney Dis* 2005; **45**: 39–47.
7. Guo ZJ, Niu HX, Hou FF *et al.* Advanced oxidation protein products activate vascular endothelial cells via a RAGE-mediated signaling pathway. *Antioxid Redox Signal* 2008; **10**: 1699–1712.
8. Peng KF, Wu XF, Zhao HW *et al.* Advanced oxidation protein products induce monocyte chemoattractant protein-1 expression via p38 mitogen-activated protein kinase activation in rat vascular smooth muscle cells. *Chin Med J* 2006; **119**: 1088–1093.
9. Zhou LL, Hou FF, Wang GB *et al.* Accumulation of advanced oxidation protein products induces podocyte apoptosis and deletion through NADPH-dependent mechanisms. *Kidney Int* 2009; **76**: 1148–1160.
10. Shankland SJ. The podocyte's response to injury: role in proteinuria and glomerulosclerosis. *Kidney Int* 2006; **69**: 2131–2147.
11. Li Y, Kang YS, Dai C *et al.* Epithelial-to-mesenchymal transition is a potential pathway leading to podocyte dysfunction and proteinuria. *Am J Pathol* 2008; **172**: 299–308.
12. Okamura DM, Pennathur S, Pasichnyk K *et al.* CD36 regulates oxidative stress and inflammation in hypercholesterolemic CKD. *J Am Soc Nephrol* 2009; **20**: 495–505.

see original article on page 1199

Mediterranean diets: are they practical in the Western world?

Aakash R. Amin[1] and James L. Bailey[2]

The incidence of metabolic syndrome (MS) in renal transplant patients is unacceptably high. Dietary intake may ameliorate or worsen the potential for the development of MS. The choice of immunosuppression also plays a role. Continued effort to find beneficial dietary combinations is essential while ongoing research evolves to find newer immunosuppressive medications with less adverse metabolic side effects.

Kidney International (2009) **76,** 1127–1129. doi:10.1038/ki.2009.378

It is well known that cardiovascular disease is a significant cause of death in renal transplant patients and may account for 47% of all deaths in this population.[1] The increased propensity for cardiovascular disease is thought to stem from the interplay of immunosuppressive medications, most notably calcineurin inhibitors and corticosteroids. The sequelae of taking these medications in the post-transplantation period include the development of weight gain, hyperlipidemia, hypertension, and glucose intolerance, which in combination describe metabolic syndrome (MS).[2,3] In addition to accelerating post-transplantation cardiovascular disease, MS has been thought to be a risk factor for chronic renal allograft dysfunction.[4] MS has been reported to be as high as 57% in the first year following transplantation.[5] MS is a dynamic disorder, and its development probably arises from the interaction of genetic makeup and lifestyle. Nafar and colleagues[6]

[1]*Department of Nephrology, Emory University, Atlanta, Georgia, USA and* [2]*Renal Division, Department of Medicine, Emory University, Atlanta, Georgia, USA*
Correspondence: *Aakash R. Amin, Department of Nephrology, Emory University Hospital, 1639 Pierce Drive NE, Renal Division, WMB 338, Atlanta, GA 30322, USA. E-mail: aamin5@emory.edu*