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., 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

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). 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. 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. 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 exaggerated glomerulosclerosis in remnant kidney and diabetic nephropathy. 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 marker for cardiovascular disease.

see original article on page 1148

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

Youhua Liu

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.
Oxidative stress (CKD, diabetes, metabolic syndrome) → AOPPs

Receptor → RAGE

CD36 Novel receptor

PKC

NADPH oxidase

Superoxide (O$_{2}^-$) generation

p53

Bax/Bcl2

Caspase activation

Podocyte apoptosis and depletion

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. 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 and thereby lead to an excessive cardiovascular risk in uremic patients.

Zhou and colleagues (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, which is about 17% of the entire glomerular podocyte population in that setting. This magnitude of podocyte apoptosis in vitro 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. 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. 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. (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. 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. 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

see original article on page 1199

Mediterranean diets: are they practical in the Western world?

Aakash R. Amin1 and James L. Bailey2

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.


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. 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). In addition to accelerating post-transplantation cardiovascular disease, MS has been thought to be a risk factor for chronic renal allograft dysfunction. MS has been reported to be as high as 57% in the first year following transplantation. MS is a dynamic disorder, and its development probably arises from the interaction of genetic makeup and lifestyle. Nafar and colleagues

1Department of Nephrology, Emory University, Atlanta, Georgia, USA and
2Renal 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