Nitro-oleic acid is a novel anti-oxidative therapy for diabetic kidney disease

Madhav C. Menon, Peter Y. Chuang, and John C. He

Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

Diabetic kidney disease (DKD) remains the leading cause of end-stage renal disease (ESRD) in the United States (4). While the number of persons developing ESRD continues to increase annually, those who have diabetes listed as a primary cause of ESRD have stayed constant while the incidence of ESRD due to diabetes among diabetic patients has declined (3, 4). These improvements in diabetes-related ESRD incidence are unlikely to be attributable to any single intervention, but rather as a consequence of widespread use of interventions that combine multiple therapeutic strategies simultaneously—lifestyle modifications, improved glycemic control, treatment of associated hypertension/dyslipidemia, and the use of renin-angiotensin-aldosterone axis blockade.

In recent years, studies have implicated intracellular hyperglycemia with metabolic byproduct accumulation, and consequent oxidative-stress-related, proinflammatory, and profibrotic pathway activation as central to organ damage in diabetics, including DKD (see comprehensive reviews in Refs. 2 and 7). Hence, in addition to treating hyperglycemia itself, the current and evolving paradigm in drug discovery for treating DKD to delay progression to ESRD is one of using modalities that either simultaneously target multiple effector pathways, or combining one or more modalities to achieve this end. Large-scale clinical trials have established the role of ACE inhibitors and angiotensin receptor blockers (ARB) in reducing proteinuria, improving renal histology, and slowing estimated glomerular filtration rate decline in DKD through antagonizing effectors’ pathways at different steps (1, 11, 12) (see review in Ref. 26). While many other anti-inflammatory, anti-oxidative, and anti-fibrotic drugs have been used experimentally or in clinical trials, none of these has advanced beyond phase III clinical trials or translated into clinical use in patients with DKD (5). For instance, targeting NF-κB-TNF-α using pentoxiphyllin has met with success in experimental models and in small-scale clinical trials of DKD (13, 14, 17). Excessive protein kinase C (PKC) activation is an early effect of intracellular hyperglycemia with multiple downstream implications (2) and inhibiting PKC using ruboxistaurin has shown promise in animal models and small clinical trials (10, 23). Advanced glycation end products has been considered as a major cause of DKD (22). However, clinical trial failed to prove this efficacy and the treatment was associated with significant side effects. Two recent high-profile study medications for treatment of DKD that failed in phase III clinical trials are sulodexide (19) and bardoxolone (20). These medications were associated with untoward adverse events. Therefore, it is critical to develop effective drugs with fewer adverse effects for treatment of DKD.

Fatty acid nitrification is mediated by reactive nitrogen oxides such as the nitrogen dioxide radical, which can originate from intracellular processes [oxidation of nitric oxide (NO) by oxygen or superoxide, reduction of nitrite by methemoglobin], or exogenously (e.g., cigarette smoke) (8). Diverse signaling properties have been attributed to nitro-oleic acid (OA-NO2), which is present in significant concentrations in human plasma implying biological significance (8). In animal models, OA-NO2 has demonstrated benefits in hypertension (28), vascular neointimal proliferation (6), obesity with the metabolic syndrome (24), and hyperglycemia in diabetes (21). Recent publications have suggested that exogenously administered OA-NO2 can cause nonselective activation of PPAR, which may in part account for OA-NO2’s biological effects (21, 24). Activation of anti-inflammatory and prosurvival nrf2-signaling has also been identified as a major effect of OA-NO2 (9).

In an issue of the American Journal of Physiology-Renal Physiology, Liu and colleagues report the efficacy of combining OA-NO2 with ARB to retard the progression of DKD in mice (16a). Twelve-week-old obese db/db C57BLKS mice treated for 2 wk with either oral losartan, OA-NO2, or ethanol (vehicle) by miniosmotic pump, or a combination of losartan with OA-NO2, the authors demonstrate a marked improvement in histological and biochemical parameters of DKD progression in the combination-treated mice compared with all other treatment conditions. Notably, these mice had DKD at baseline as evidenced by proteinuria. No differences in weight gain, kidney weight/body weight ratio, or hyperglycemia were observed within the four obese treatment groups at the end of 2 wk. While significant reductions in glomerulosclerosis scores were seen in all treatment groups compared with vehicle, the greatest reduction was seen with combination treatment. Significant reduction of proteinuria, preservervation of podocyte number, and prevention of profibrotic extracellular matrix marker production were encountered in the combination treatment group. From a mechanistic standpoint, the authors attributed the salutary effects of the OA-NO2-Losartan combination treated to a more robust suppression of oxidative stress and the inflammation compared with all other groups.

Some issues are to be noted. A prior study suggested significantly improved hyperglycemia with OA-NO2 in Ob/Ob C57Bl6 mice that was comparable with the use of thiazolidinediones (TZDs) (21). In the current study, no difference in glycemia was observed in any of the OA-NO2 groups. This may reflect differences in dose/duration of OA-NO2 between the two studies. In the present study, ARB alone did not have any significant effects on proteinuria, which is not consistent with previous studies. Finally, PPARy activation with longer duration of OA-NO2 treatment may be accompanied by adverse cardiovascular effects observed with PPARy agonists (i.e., TZDs) (18), which will need to be addressed before clinical trials. It also remains to be determined whether this combination therapy could reverse the kidney injury of DKD.

Overall, this is an important study. OA-NO2 is a newly identified endogenous product with potent anti-oxidant and anti-inflammatory properties and has demonstrated a favorable safety profile in animal studies. These features make it an attractive agent for treating DKD. The combination of a renin-
angiotensin system inhibitor and OA-NO2 provides better outcome data suggesting that this strategy could be developed to treat DKD patients who are already treated with ACEI or ARB. This study along with other studies of OA-NO2 use in nondiabetic kidney injury models [adrinamycin nephropathy (16), ischemia-reperfusion injury (15), endotoxin-mediated renal injury (25)] suggests promise for this combination not only in DKD but also in other kidney diseases. However, this would need more extensive experimental validation with specific description of mechanism of action in kidney disease, clarification of safety profile, and improved modes of administration before phase I trials in humans.

REFERENCES


