Sex Differences and Renal Protection: Keeping in Touch with Your Feminine Side

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Recognition of the fundamental roles played by sex-specific factors in health and disease led to the 1993 National Institutes of Health (NIH) Revitalization Act that mandates that National Institutes of Health researchers include women in clinical studies and that results be analyzed by sex or gender.1 It took another 20 years to advise the implementation of similar policies to preclinical research, such as the equal inclusion of male and female animals and analyses of animal and cell data by sex, suggesting that discovery of key sex differences may inform subsequent clinical studies.2 Whereas the initial focus of sex differences was on cardiovascular disease, their role in the susceptibility to, and progression of, renal disease has increasingly been recognized, with a growing interest in the possible renal-protective role of female sex and hormones.

Large epidemiologic studies indicate that the incidence of ESRD is higher in men compared with women across the lifespan.3 In animal models of renal injury, males are commonly affected more than females, thus resulting in male animals being used more often in studies of the mechanisms of renal injury. A recent study has indicated that tolerance to ischemia-reperfusion injury is increased in female compared with male mice, and that female mice receiving supplemental estrogen before ischemia were protected further.4 Consequently, the possible mechanisms that underlie the renal-protective role of female sex seem to be related to estrogen, and therefore limited to premenopausal women. This is supported by clinical studies which have demonstrated that premenopausal women, as compared with aged-matched men, are protected from renal and cardiovascular disease; this protective effect seems to be lost with aging and menopause.5 However, the mechanisms by which estrogen confers protective renal effects are not well understood.

Two studies in this issue extend our knowledge of the renal-protective effects of estrogen, by providing evidence that cyclic changes in female reproductive hormones, including estrogen, in premenopausal women may be protective against renal injury in general,⁶ and that estrogen may be a potential therapeutic option for renal injury in diabetic nephropathy, in particular.⁷

Seppi et al.⁶ investigated the urinary excretion of renal proximal tubular enzymes—fructose-1,6-bisphosphatase (F-1,6-BPase) and glutathione-S-transferase-α (GSTα)—during the female reproductive hormone cycle. They found that premenopausal, naturally ovulating women, but not men or postmenopausal women, demonstrated two distinct peaks in the urinary excretion of F-1,6-BPase and GSTα that followed the rhythmic hormonal changes of the menstrual cycle, occurring consistently within 7 days after ovulation or the onset of menstrual bleeding. This was not accompanied by changes in the urinary concentrations of the proteins that are reabsorbed by the tubular epithelium (such as albumin), suggesting that enzymuria was not associated with proximal tubular dysfunction. They argue that estrogen exerts proliferative and antiapoptotic effects on proximal tubular cells during the phases of the menstrual cycle characterized by high estrogen levels. In turn, decreases in estrogen, which occur after ovulation and before the onset of menstrual bleeding, may result in proximal tubular cell death, as characterized by urinary F-1,6-BPase and GSTα excretion. The authors postulate that the fluctuating levels of female sex hormones translate into transient increases in tubular cell turnover that renders proximal tubular cells more resistant to renal damage, and that the urinary excretion of proximal tubular enzymes reflects this.

Several provocative questions with respect to female renal health and disease can be asked on the basis of the results of this study. First, given the high levels of sex hormones during pregnancy, is it possible that pregnancy-related alterations in renal function, e.g., the increase in GFR, may be, at least in part, related to the estrogen-mediated proliferative and antiapoptotic effects on proximal tubular cells? Second, some, but not all, renal diseases progress during pregnancy, despite the presence of high estrogen levels, raising the possibility that estrogen-protective effects are disease-specific. Alternatively, the protective estrogen effects in pregnancy may be offset by the inflammatory and hypercoagulable milieu that develops as a physiologic adaptation to normal pregnancy and is exaggerated further in pregnancies complicated by renal disease. Third, it is common for women with advanced renal disease to become amenorrheic. Does the absence of normal menstrual cycles/ovulation in CKD patients lead to a vicious cycle of CKD→estrogen dysregulation→CKD, and would hormonal...
therapy slow the progression of CKD? Finally, the authors suggest that enhanced repair capacity may be potentiated by chronic exposure to cyclic hormonal changes during the premenopausal years. However, several studies have suggested that even temporary, short treatment with estrogen, rather than exposure over the reproductive lifetime, has a renal-protective or therapeutic effect, including the study by Inada et al.\textsuperscript{7} in this issue.

Inada et al.\textsuperscript{7} argue that administration of 17\textbeta-estradiol (E2) is an effective treatment of diabetic nephropathy, even in the presence of glomerulosclerosis. They used a diabetic transgenic mice model generated by β cell overexpression of inducible cAMP early repressor that has previously been shown to result in severe early-onset diabetes and diabetic renal injury in male, but not female, mice.\textsuperscript{8} Citing clinical evidence for a lower risk of diabetic nephropathy in premenopausal compared with postmenopausal women, they hypothesized that female inducible CAMP early repressor transgenic mice were protected from diabetic renal injury by circulating E2 levels. In their study, they treated male mice with E2 pellet implantation in doses that adjusted the E2/androgen ratio to that observed in female transgenic mice. Treatment with E2 ameliorated renal injury, both in early- and late-stage diabetic nephropathy, and was more effective than either orchiectomy or islet cell transplantation.

Several epidemiologic and animal studies have confirmed the role of sex and sex hormones in the development of diabetes and progression of diabetic nephropathy. The protective role of female gender parallels estrogen levels, as demonstrated by a steep increase in the incidence of diabetes during the premenopausal and menopausal years.\textsuperscript{9} A study of ovariectomized \textit{db/db} mice, a model of type 2 diabetes mellitus, undergoing an 8-week E2 treatment demonstrated reduced hyperglycemia, reduced albuminuria, and weight gain.\textsuperscript{10} Further, the authors of animal studies of castrated and ovariectomized rats have argued that both the absence of estrogens and the presence of androgens are risk factors for glomerular injury.\textsuperscript{11,12} Inada et al.\textsuperscript{7} investigated the renal effects of E2 with or without orchiectomy and concluded that E2 was more effective than orchiectomy alone in controlling hyperglycemia, increasing the number of β cells, and reducing glomerular injury. The authors proposed that E2 supplementation that modulates the E2/androgen ratio is a promising therapeutic option for diabetic nephropathy. Their conclusions need to be critically evaluated with respect to E2 safety and efficacy as a therapeutic agent.

The authors of several animal studies have argued that the effects of estrogen on diabetic nephropathy are not always beneficial and that, at least in certain animal strains, estrogen may contribute to the development of glomerulosclerosis.\textsuperscript{13,14} The controversy has been fueled further by clinical studies that have argued that exogenous estrogen may be harmful to the kidneys, as suggested by a Canadian study of almost 6000 women, which concluded that estrogen therapy in postmenopausal women was associated with loss of renal function.\textsuperscript{15} However, this study had several limitations, including the failure to control for important confounders, such as hypertension and obesity. More recently, data are becoming available regarding the effects of cross-sex hormone treatment on transgender women (persons who were identified as males at birth, but who identify as females) who receive estrogen in order to develop female secondary sex characteristics. A 6-month course of estrogen therapy in transgender women resulted in significant reductions in BP compared with baseline\textsuperscript{16} and decreases in plasma homocysteine levels—a risk factor for atherosclerotic and thrombotic disease.\textsuperscript{17} These beneficial estrogen effects on cardiovascular disease risk factors may translate into reduced renal disease risk as well (particularly the favorable BP effects), but may not be clinically useful for the general patient population, due to the unacceptable feminizing side effects in men and the increased breast and uterine cancer risks in women. A safer treatment option would be raloxifene, a selective estrogen receptor modulator. Treatment with raloxifene was proven to be renal-protective, both in a post hoc analysis of postmenopausal women with osteoporosis\textsuperscript{18} and in a randomized, placebo-controlled trial of postmenopausal women with diabetes and albuminuria.\textsuperscript{19} Animal studies have shed light on the possible mechanism of the protective effects of raloxifene in the kidney: in ovariectomized \textit{db/db} mice, raloxifene inhibited TGF β-1-induced fibronectin transcription.\textsuperscript{10} Raloxifene, to date, has been used both in men and women for the treatment of neurocognitive deficits in schizophrenia, and has been proven to be safe and effective in improving attention, memory, and learning.\textsuperscript{20}

In conclusion, two papers in this issue demonstrate that endogenous estrogen may exert protective renal effects\textsuperscript{6} and estrogen supplementation may be an effective treatment strategy for diabetic nephropathy.\textsuperscript{7} Additional studies are required to elucidate the clinical importance of these findings. In view of the findings of Seppi et al.,\textsuperscript{6} consideration should be given to estrogen supplementation in a manner that mimics estrogen variability in premenopausal women. This may be particularly important for proximal cell turnover and repair and, ultimately, increased resistance to renal injury.

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DISCLOSURES

None.

REFERENCES