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See related article, "Antidiuretic Action of Collecting Duct (Pro)Renin Receptor Downstream of Vasopressin and PGE_2 Receptor EP_4," on pages 3022–3034.

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

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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.*[7] in this issue.

Inada *et al.*[7] argue that administration of 17β-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.[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 perimenopausal and menopausal years.[9] A study of ovariectomized *db/db* mice, a model of type 2 diabetes mellitus, undergoing an 8-week E2 treatment demonstrated reduced hyperglycemia, reduced albuminuria, and weight gain.[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.[11,12] Inada *et al.*,[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.[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.[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[16] and decreases in plasma homocysteine levels—a risk factor for atherosclerotic and thrombotic disease.[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[18] and in a randomized, placebo-controlled trial of postmenopausal women with diabetes and albuminuria.[19] Animal studies have shed light on the possible mechanism of the protective effects of raloxifene in the kidney: in ovariectomized *db/db* mice, raloxifene inhibited TGF β-1–induced fibronectin transcription.[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.[20]

In conclusion, two papers in this issue demonstrate that endogenous estrogen may exert protective renal effects[6] and estrogen supplementation may be an effective treatment strategy for diabetic nephropathy.[7] Additional studies are required to elucidate the clinical importance of these findings. In view of the findings of Seppi *et al.*,[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.

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See related articles, "Adjusting the 17β–Estradiol-to-Androgen Ratio Ameliorates Diabetic Nephropathy," and "Sex Differences in Renal Proximal Tubular Cell Homeostasis," on pages 3035–3050 and 3051–3062, respectively.

ESRD Payment Reform: First Do No Harm

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"Bureaucracy defends the status quo long past the time when the quo has lost its status – Laurence J. Peter (*American educator & writer; 1919–1988)*"

The continued growth of the number of patients receiving RRT levies not only a personal toll on families and communities, but also an increasing financial burden on Medicare. With patients with ESRD accounting for <1% of the total Medicare population but consuming nearly 7% of Medicare costs,[1] there is a crucial need to explore new strategies to advance value-based care. The challenge of balancing cost constraints while maintaining quality of care continuously lingers over the nephrology community. The introduction of new health care policies and regulations are designed to enhance the value of care by improving patient outcomes and/or reducing costs. To ensure there are not unintended consequences of such policies (*Primum non nocere* – first, do no harm), a careful evaluation of their impact is needed. Even if there are formal evaluation strategies in place, it is often incumbent on the medical community to conduct independent analyses, especially when there could be conflicting effects of policies on patient and financial outcomes. In this issue of the *Journal of the American Society of Nephrology* (*JASN*), Chertow *et al.* take on such a challenge.[2]

In an effort to balance quality of care and costs to optimize the value of renal health care delivery, the US Congress passed the Medicare Improvements for Patients with Providers Act (MIPPA HR 6331) in 2008, which mandated reform of Medicare reimbursement policies. The Centers for Medicare and Medicaid Services (CMS) released a final ruling for implementation of the ESRD prospect of payment system in July of 2010[3] that was subsequently implemented in January of 2011.[4,5] This new, bundled payment for ESRD was developed on the same principles that led to the original "Composite Rate" dialysis payment introduced in 1983 and transformed reimbursement to one set payment per dialysis treatment, including ESRD lab tests, intravenous medications (*e.g.,* erythropoiesis stimulating agents [ESAs], vitamin D, and iron), and oral medications with intravenous equivalents.[6] To lower Medicare expenditures, the 2011 bundled payment for ESRD reduced payments to ESRD facilities by 2% overall and eliminated incentives to the overuse of previously profitable, separately billable drugs. In particular, ESAs changed from being separately billable to being part of the bundled payment. This was prompted, in part, due to the high costs of ESA treatment, and in part because controlled trials demonstrated that targeting hemoglobin levels of ≥13 g/dl led to higher rates of mortality, cardiovascular events, and stroke in patients with CKD.[7–9] These studies also led to the US Food and Drug administration to require a modification of ESA product labels, which were released in June of 2011. This replaced the conventional hemoglobin target of 10–12 g/dl with recommendations to reduce or interrupt dosing as the hemoglobin approaches or exceeds 11 g/dl.[10]

Thus, the combination of the introduction of Medicare ESRD payment reform (in January of 2011) and changes in ESA product labeling (in June of 2011) rapidly led to a 29%–52% reduction in the use of ESAs in dialysis patients across different dialysis organizations.[11] However, the new bundled payment model also raised many concerns about the impact of managing trade-offs that could affect facility and/or provider behaviors and lead to unintended adverse consequences,[12] including worse outcomes for patients with ESRD due to the potential for undertreatment in terms of dialysis time, anemia management, and mineral and bone disorders.[4] In fact, the American Society of Nephrology (ASN) called for close monitoring of not only intermediate quality care outcomes such as lab values, but downstream clinical outcomes such as hospitalizations and mortality.[4] Several studies have subsequently examined the impact of bundled payment on intermediary outcomes and suggest that overall, the nephrology community has done an excellent job in maintaining the quality care for patients with ESRD. A recent analysis by Swaminathan *et al.* found the reduction in ESA use among dialysis patients was limited to those with a hematocrit >36%, with little change in use among patients with hematocrit ≤36%, suggesting that the impact on ESA reduction has appropriately been among patients who are least likely to benefit from the use of these agents.[13] In a cross-sectional analysis, Turenne *et al.* reported trends in ESRD quality care measures in 132 facilities in the Dialysis Outcomes and Practice Patterns Study from August of 2010 to December of 2011.[14] Not unexpectedly, they found that not only did mean hemoglobin levels fall from 11.5 to 11.0 g/dl, along with erythropoietin doses falling by >25%, but mean serum parathyroid hormone levels rose

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