Sex and Gender Differences Deserve More Study in Kidney Diseases

By Ruth Jessen Hickman

Before the National Institutes of Health (NIH) Revitalization Act, women were largely underrepresented in clinical trials, partly out of concerns for teratogenic effects. The act, passed in 1993, made it mandatory that clinical trials funded through NIH include data from women and minorities (1).

The percentage of women included in clinical trials has improved significantly since that time (2), although women are still underrepresented with respect to disease prevalence in some reports (3). However, data from men and women are often still aggregated together, and analyses based on sex are often not reported.

Clinical studies often lack sufficient statistical power to examine sex differences, said Christine Maric-Bilkan, PhD, a program director of the Division of Kidney, Urologic, and Hematologic Diseases in the NIH’s National Institute of Diabetes and Digestive and Kidney Diseases. “There should be no barriers to reporting data by sex, and many journals are in fact insisting on papers including data by sex, so that should help,” she said.

Females have also been underrepresented in the scientific research underlying these clinical trials. For example, most basic science studies are still performed on male kidneys, and much of what is known about basic physiology and pharmacokinetics is derived from studies performed in males (4). In 2015, the NIH released recommendations that sex be considered in the research design, analyses, and reporting of preclinical studies, although this was not mandated (5).

However, studies of sex differences are still scarce. “The vast majority of preclinical studies are being conducted in males, either in cells or animals,” said Maric-Bilkan. “Unfortunately, this trend is not unique to any one research discipline or field, as a similar male bias has been reported across the board: neuroscience, immunology, cardiovascular, renal, etc.”

Still, some fields have made more research progress in this area than others. “If we compare ourselves to cancer or cardiology research, we in nephrology are a bit behind in terms of understanding how sex hormones and sex hormone receptors are playing a role in these diseases,” said Eman Gohar, PhD, an instructor in the Division of Nephrology at the University of Alabama at Birmingham. One of her areas of expertise is sex differences in kidney diseases.

Interim Report on Race and Kidney Function Addresses Process

By Eric Seaborg

The National Kidney Foundation-American Society of Nephrology (NKF-ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease released its highly anticipated interim report at the start of April. Published concurrently in JASN and the American Journal of Kidney Disease (AJKD), the report lays out the process the task force is following.

It will take a couple more months to formulate the recommendations, according to a joint statement from the presidents of ASN and NKF, issued on March 9, 2021.

Although many stakeholders expressed hope for a recommended replacement for the use of a race factor in estimated glomerular filtration rate (eGFR) as soon as possible, the news that this report lacked recommendations was greeted mainly with an acknowledgment that the original timeline was overly ambitious for the complex undertaking. “Although I think I (and the medical community) all hoped for immediately actionable recommendations, it is understandable that this is a challenging task in the very short term,” said Eman Gohar, PhD, an instructor in the Division of Nephrology at the University of Alabama at Birmingham. One of her areas of expertise is sex differences in kidney diseases.

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Researchers are increasingly realizing that sex and gender influence kidney function in both normal and pathophysiologic conditions. Noting that there is much to learn about the mechanisms underlying these differences, Maric-Bilkan stated: “There is increasing recognition that examining sex and gender differences in disease pathophysiology could lead to development of sex-specific therapeutic treatments.”

Sex versus gender

To navigate this topic, it is important to clarify sex and gender. The US Institute of Medicine guidelines define sex differences as biologic differences between men and women. These include differences due to sex hormones but also differences due to chromosomes and sex-specific gene expression. Gender refers to an individual’s sense of them- selves as a male or female in society (6). Although people often misunderstand the effects of sex hormones when discussing sex differences in this context, epidemiologic differences between the sexes in kidney disease incidence or progression might reflect a whole host of factors, including socially ascribed ones.

But differences due to sex hormones, particularly estrogen, have been the focus of a great deal of the existing research. It is now well recognized that sex hormones have biologic effects extending beyond the reproductive system. Different kidney-protective effects for estrogen and testosterone are widely found in many different parts of the body, including the kidney (4). A large body of research implicates sex steroid hormones as major contributors to normal and pathophysiologic sex differences in the kidney. The classic estrogen receptors, ERα and ERβ, act in the cell nucleus of kidney cells to stimulate gene expression. More recently, researchers have discovered a G-protein-linked estrogen receptor that can initiate more rapid signaling in kidney cells. Much remains to be learned about the exact location and intended function of these estrogen receptor subtypes in kidney cells, as well as for subtypes of androgen receptors (4).

Premenopausal women appear to be somewhat protect- ed from kidney disease compared with age-matched men across all kidney-protective pathways. This relative protection seems to disappear during menopause. Women who undergo oophorectomy have a higher incidence of chronic kidney disease (CKD) as well, suggesting a protective role for estrogens. Studies in animal models also strongly support the role of estrogens, particularly estradiol, as an important secretory stimulus for the kidney. But differences due to sex hormones, particularly estrogens, have been underscored for the role of estrogens in maintaining sex differences in disease pathophysiology and could lead to development of sex-specific therapeutic treatments.

What the discrepancies in prevalence?

The reasons for these discrepancies continue to be traced out, but multiple mediating factors have been proposed. The use of a single cutoff point of estimated glomerular filtration rate (eGFR) to define CKD might lead to an over-diagnosis of CKD in women because it may not account for normal physiologic differences in rates (7). Differences due to sex hormones; sex chromosomes; renal heredity; and factors such as smoking and health-styles use, including earlier initiation of dialysis in men compared with women, may also account for these discrepancies (8). In some situations, social and cultural factors may mask underlying biologic and physiologic tendencies, making int- erpretation difficult. “We need to acknowledge differences in access to care, compliance with medications, speed of referral to dialysis, and discrepancies in kidney transplanta- tion in men versus women,” Gohar said.

Maric-Bilkan also underscored the need for more rigor- ous, well-designed observational studies that focus on defin- ing sex differences in treatment and progress and that consider the sex-specific categorization of kidney disease severity. “These studies should address the role of sex-related biologic differences and differences in psychosocial, lifestyle, and other factors,” she said. “They should take into account the menopausal status of the patient, hor- mone therapy use, and history of use of oral contraceptives, which may also affect kidney disease progression.”

The pathways potentially mediating the nephroprotective effects of estrogens are still being elucidated. Researchers know, for example, that sex hormones modu- late endothelin, a potent vasoactive factor with disease im- plications for essential hypertension and kidney disease. An- imal studies demonstrate important sex-related differences in endothelin receptor subtype expression, abundance, and function (9).

Immune signaling pathways have also been shown to be affected by sex and sex steroids, and these might also influ- ence differences in kidney pathophysiology. Other potential avenues being explored include differential modulation of reactive oxygen species via redox signaling pathways (10). A research article published by Gohar and colleagues in the Journal of the American Heart Association demonstrates a novel function for the G-protein-coupled estrogen receptor in the kidney (10). Its activity was found to have a direct impact on sodium reabsorption, influencing blood pressure and kidney excretory function in female rats.

One challenge with working with estrogen as a poten- tial therapy is its broad presence in multiple organ systems and resulting off-target effects. The potential risks/benefits of hormone replacement therapy in menopausal women were brought into question by the famous Women’s Health Initiative outcomes, which unexpectedly raised concerns about the cardiovascular impact of such supplementation. Although later analyses have highlighted the importance of properly timing hormone replacement therapy and have raised questions about study design, many clinicians and patients still have concerns about its risks and benefits (11).

Treatments targeting specific subtypes of estrogen re- ceptors may prove fruitful research avenues. For example, Gohar said, one could focus on the G-protein-coupled estrogen receptor that has been shown to elicit protective actions in the cardiovascular and renal systems in females, which might theoretically make them viable drug targets in postmenopausal women.

Much might be learned at the basic science level by stud- ying models of kidney disease in which the female kidney is relatively protected, such as hypertension, acute kidney injury, and diabetic kidney disease. Uncovering the mecha- nisms that underlie this protection may ultimately contrib- ute to the development of novel therapeutic choices in both women and men.

Gohar pointed out that women’s kidneys are physiologi- cally equipped to handle pregnancy, which poses huge chal- lenges in fluid and electrolyte management. She suggested that improving our knowledge of female kidney physiology may ultimately lead to better understanding of preclampsia and broader insights into pathologic changes in the kidney.

In addition to investigations into the contribution of sex hormones, research into other physiologic and social fac- tors influencing epidemiology will be key. “Studies in other fields have brought to attention that X- or Y-linked genes, parental imprinting, or X mosaicism also contribute to sex differences,” said Maric-Bilkan.


6. Maric-Bilkan K, et al. Differences in drug absorption, distribution, and metabolism as cause of side effects in women (12). Women and men may experience different drug exposure resulting from differ- ences in drug absorption, distribution, and metabolism as well as body weight. More research attention to these issues might allow for drug approvals in subsets of the population or might point the way toward adjustments of drug dosage in women that might lower toxicity. Such study designs present research challenges, especially in women, Maric-Bilkan said. A better under- standing of these issues would provide important data to help move toward more personalized medicine. Ideally, new therapeutic approaches to kidney disease could be tailored based on patients’ gender and hormonal status.

“The more studies examining sex differences in renal function and pathophysiology, the more information we will have on what pathways may be targeted for drug develop- ment. Also, better understanding of disease pathophysi- ology could inform how existing therapies may be adapted and optimally used in both women and men,” Maric-Bilkan said.

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