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Sex and the kidneys: current understanding and research opportunities

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Abstract

Concerns regarding sex differences are increasingly pertinent in scientific and societal arenas. Although biological sex and socio-cultural gender are increasingly recognized as important modulators of renal function under physiological and pathophysiological conditions, gaps remain in our understanding of the mechanisms underlying sex differences in renal pathophysiology, disease development, progression and management. In this Perspectives article, we discuss

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specific opportunities for future research aimed at addressing these knowledge gaps. Such opportunities include the development of standardized core data elements and outcomes related to sex for use in clinical studies to establish a connection between sex hormones and renal disease development or progression, development of a knowledge portal to promote fundamental understanding of physiological differences between male and female kidneys in animal models and in humans, and the creation of new or the development of existing resources and datasets to make them more readily available for interrogation of sex differences. These ideas are intended to stimulate thought and interest among the renal research community as they consider sex as a biological variable in future research projects.

In 1993, the US Congress passed ‘The National Institutes of Health (NIH) Revitalization Act’, which mandated that women and minorities be included in clinical trials funded through the NIH[1]. Despite this mandate, women remain under-represented in clinical trials in the USA. For example, between 2005 and 2015, representation of women in cardiovascular disease trials fell below a participation-to-prevalence ratio of 0.8 (REFS[2,3]) (no comparable data for trials in renal diseases exist). Moreover, when women are included, gender-based reporting of results is often lacking[4]. In 2015, the NIH released a notice, “Consideration of Sex as a Biological Variable in NIH-funded Research”, which outlined the expectation that sex will be considered in research design, analyses and reporting in preclinical studies[5].

These NIH policies and initiatives raised awareness regarding differences in human disease according to sex and gender[2], but much remains to be learned about sex and gender differences in disease pathophysiology, including renal diseases.

Many controversies exist regarding the contributions of both biological sex and socio-cultural factors in the pathophysiology, prevalence and progression of renal diseases. For example, although it has been argued that premenopausal women are relatively protected from non-diabetic renal disease compared with age-matched men[6–8], epidemiological and clinical studies over the past decade depict a more complex picture. Some studies have suggested that female sex and/or gender might adversely affect renal pathophysiology, disease progression and outcomes. Compared with men, more women progress to stage G3 chronic kidney disease (CKD), they have reduced access to deceased donor transplantation and poorer quality of life while on renal replacement therapy (RRT)[9–11]. Reports also exist of female sex as a protective factor in renal disease and studies in animal models have suggested that oestrogens might exert renoprotective effects in various models of non-diabetic and diabetic renal disease[12–15]. However, the influence of sex on disease development and progression might not be limited to sex hormone interactions — whether sex chromosomes or other genetic and epigenetic events influence renal function independently or in concert with sex hormones remains poorly understood.

Recognizing the need to address these controversies and the gaps related to the understanding of sex and gender differences in renal diseases, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a workshop entitled “Sex and the Kidneys” in July 2017 at the NIH in Bethesda, MD, USA. The workshop gathered experts from the fields of nephrology, endocrinology, imaging and sex differences in renal

and other diseases (including cardiovascular disorders, diabetes, obesity and hypertension) to discuss the current state of the science and identify opportunities for future research. In this Perspectives article, we highlight the opportunities for clinical, basic and translational research into sex differences in renal disease as well as the potential tools and resources for conducting this research that were identified during the workshop (BOX 1; FIG. 1).

For the purposes of this article, we define sex and gender according to the US Institute of Medicine guidelines, which describe sex differences as biological differences between men and women, such as differences in sex chromosomes, sex-specific gene expression and sex hormones. Gender refers to one's sense of self as male or female in society, with differences including factors such as lifestyle, environmental influences and nutrition[16]. Although differences in gender and sex were considered equally important, discussions during the NIDDK workshop were predominantly centred around sex (that is, biological) differences. However, it should be noted that the effects of sex and gender are often intertwined and thus a clear distinction between the two might not be possible.

Clinical research

Numerous inconsistencies exist in findings regarding the association between biological sex and renal disease, and many attempts have been made to determine the nature of this association. Complex interactions among biological, cultural and socio-economic factors are thought to underlie some of these differences, but the precise mechanisms are not fully understood. Examining and reporting sex and gender differences is vitally important as they provide a foundation and scientific premise for studies in humans and animals. Furthermore, a better understanding of how sex contributes to disease aetiology, mechanisms and epidemiology might guide future clinical research on potential sex-specific therapies for renal diseases. In discussing these issues, the workshop participants identified the following priorities for future research.

Epidemiology of sex differences.

CKD (defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2) has been reported to be more common in women than in men[17–21]; however, the validity of this conclusion has been questioned. Although the sex difference in bias in the equations used to estimate GFR is relatively small, the use of a single eGFR cut-off to define CKD might lead to over-diagnosis of CKD in women without some adjustment for normal gender-specific decline in eGFR with ageing[22,23]. Nearly two decades ago a meta-analysis suggested that sex influences the rate of progression of non-diabetic CKD and that female sex is reno-protective[8]. Experimental models of non-diabetic CKD clearly show a protective effect of oestrogen and a deleterious effect of testosterone, but the data in humans are less clear[24]. Reports of a higher incidence of CKD in women than in men also contrast with the observation that incident end-stage renal disease (ESRD) is more common in men than in women[25–27]. Possible explanations for this apparent paradox are faster progression of renal disease in men than in women and/or disparities in health care delivery that lead to earlier initiation of dialysis in men, meaning that more women than men with stage 5 CKD die without having initiated RRT. The authors of a 2019 systematic review of more than 30

studies that reported sex-stratified data concluded that renal disease progresses more rapidly in men than in women[23]. However, alternative interpretations of these data are reasonable, because many of the studies included used ESRD as an end point, which is a subjective outcome measure that may be influenced by non-biological factors. Moreover, even among studies that used the change in the slope of eGFR as an end point, progression of CKD might not only reflect biological differences between the sexes but also differences in lifestyle, cultural and socio-economic factors that are affected by gender[28]. Currently available data are thus insufficient to ascertain how sex and gender-related differences in disease progression or delivery of RRT might contribute to the observed sexual dimorphism in the incidence of ESRD.

The conflicting data in reports related to sex and the progression of CKD underscore the need for more rigorous, well-designed observational studies that focus on defining sex differences in disease development and progression, as well as considering the sex-specific categorization of renal disease severity. These studies should address the role of sex-related biological differences and differences in psychosocial, lifestyle and other factors, and take into account the menopausal status of the patients, hormone therapy use and history of the use of oral contraceptives, which may also affect renal disease progression. However, capturing data on gender identity, which would help to isolate the effects of biological processes related to sex chromosome endowment at birth from subsequent complex inputs that result in gender identity, is not common in clinical studies. Such epidemiological studies might generate novel hypotheses related to the mechanisms underlying sex differences in disease pathophysiology that could be explored in future clinical and basic research.

Core data elements.

The presence of ovarian hormones and/or the absence of testosterone have been proposed as potential mechanisms underlying the perceived relative protection of females against the progression of renal disease. This theory is supported by the observation that younger women have a lower incidence of ESRD and slower progression of CKD than men[8], but this advantage dissipates, at least according to some studies, after menopause[6]. Moreover, premenopausal women who undergo bilateral oophorectomy are at a higher risk of developing CKD than premenopausal women with intact ovaries[29], an observation that is also supported by studies in animals[30,31]. In addition, some studies have suggested that the selective oestrogen receptor modulator (SERM), raloxifene, might slow CKD progression[32], thus supporting the notion that oestrogens are renoprotective. These observations suggest a possible link between sex hormones and renal disease development or progression. However, studies examining this link are limited by the scarcity of relevant data, including age at menarche, menopausal status and use of oral contraceptives or hormone replacement therapy in female participants. This lack of data highlights the need to develop standardized core data elements and outcomes that incorporate key life cycle components for both women and men who participate in clinical studies.

Basic science research

Despite evidence that biological sex influences the course, prevalence and incidence of several renal diseases, little is known about the cellular and molecular mechanisms underlying these differences. One reason for this lack of knowledge is that most basic science studies are conducted using male kidneys. Indeed, in three leading journals that publish research on kidney physiology and pathophysiology, male:female ratios in basic science studies are 5:1 (*American Journal of Physiology-Renal Physiology*), 11:1 (*Kidney International*) and 16:1 (*Journal of the American Society of Nephrology*)[33].

In the few studies that have examined sex differences in renal diseases, the focus has predominantly been on examining the renoprotective effects of female sex hormones and SERMs[12–15]. In females, administration of SERMs or 17β-oestradiol (E_2), which binds oestrogen receptor-α (ERα), attenuates albuminuria, podocytopathy and tubulointerstitial injury, and improves renal function in several rodent models of renal disease[14,34–40]. By contrast, inhibition of oestrogen synthesis with the aromatase inhibitor anastrozole partially attenuates renal injury in male streptozotocin-induced diabetic rats[41]. Moreover, in the streptozotocin-induced model of diabetic kidney disease in males, treatment with testosterone is renoprotective, an effect mediated through the androgen recepto[42]. By contrast, in experimental models of hypertension-associated renal injury in male rats, castration decreases blood pressure and renal vascular resistance while increasing glomerular filtration rate[43,44]. These studies demonstrate that sex hormones have an important role in the development and progression of renal diseases, at least in experimental models.

Although additional studies to increase understanding of the role of sex hormones in renal pathophysiology should be encouraged, the effects of other factors that might contribute to sex differences in renal diseases, such as sex chromosomes and the effects of sex-specific gene expression on autosomes, also need to be investigated. In the context of hypertension, the few studies that have examined these factors showed that, in addition to the effects of gonadal hormones on blood pressure, X-linked and Y-linked genes, parental imprinting and X chromosome mosaicism contribute to sex differences in hypertension-associated renal injury[45]. The following section articulates some specific opportunities for future research related to sex differences in renal pathophysiology.

Renal physiology.

Over the past three decades, many studies have reported sex differences in basic renal structure and function in experimental models and in humans (TABLE 1). For example, studies in humans and rodents have demonstrated that total renal mass and the renal cortex and proximal tubules are larger in males than in females[46–48]. By contrast, the renal medulla seems to be larger in female than in male Wistar-Kyoto rats[48]. The contribution of these structural differences to sex-related variation in renal physiology or progression of CKD remains unclear. For example, although the medulla is larger and thick ascending limbs are longer in females, urine concentration is greater in males; maximum urinary concentrating ability after 48 h of dehydration does not differ between sexes[48]. Total vascular resistance per glomerulus is greater in females, whereas urine protein excretion is higher in males[49–51].

The higher renovascular resistance in female Munich-Wistar rats might protect the glomerulus from hyperfiltration-induced injury by preventing fluctuations in glomerular blood pressure[50].

Sex differences in the expression of renal glucose[52] and sodium transporters[53], water channels[53,54] and organic anion transporters[55,56] have also been reported (TABLE 1). A 2018 study developed sex-specific computational models of solute and water transport in the proximal convoluted tubule of the rat kidney to investigate the functional implications of sexual dimorphism in transporter patterns[57]. Simulations from this study predicted that 70.6% and 38.7% of the filtered volume are reabsorbed by the proximal tubule of the male and female rat kidneys, respectively. This lower fractional volume reabsorption in females might result from their smaller transport area and lower expression of aquaporin 1. This study also showed sex differences in sodium reabsorption and sodium-glucose cotransporter 2 (SGLT2) expression levels[57]. The reportedly greater SGLT2 expression in females than in males might compensate for their lower tubular transport area and enable them to achieve a hyperglycaemic tolerance similar to that of males[57].

A single, easily accessible reference portal that collates existing data on sex-related differences in normal renal structure and function would be a valuable research resource. Such a virtual library, which could be integrated, for example, into the existing NIDDK Information Network (dknet) or other existing data portals, would provide basic investigators with a comprehensive overview of differences reported in existing preclinical models and inform future experimental directions. The portal could also include relevant epidemiological data from large human cohorts to inform hypothesis-testing at the mechanistic level in preclinical models. Furthermore, information on animal age (for example, pre-pubertal or post-reproductive age), as well as the stage of oestrous cycle and parity in females, should also be included.

Sex hormone receptors in the kidney.

Sex hormone receptors, namely the oestrogen and androgen receptors, have been extensively studied in the reproductive, cardiovascular and central nervous systems[58–60], but a full appreciation of the cell types that express these receptors in the kidney has not been achieved. Sex hormones are thought to exert their effects through their classical, intranuclear receptors. However, studies from the past few years have shown that oestrogens can also bind to membrane-associated receptors[61]. Data on the localization and function of sex hormone receptors, especially the extranuclear steroid receptors in the kidney, are scarce. This information is crucial to the design of mechanistic studies that focus on the renal compartments that are most likely to mediate sex-specific effects on disease phenotypes. Current molecular probes for oestrogen and androgen receptors, as well as their co-activators and repressors, need to be validated in renal tissue and the results comprehensively reported. If existing probes are inadequate, then new ones need to be developed that recognize these receptors in different kidney cell types.

Many sophisticated genetic models of sex hormone receptor insufficiency already exist[62,63], but they have not been carefully phenotyped for renal end points. For example, although many global sex hormone receptor knockouts in mouse models lack renal phenotypes, it is

conceivable that abnormalities may only become evident under physiological stress or with comorbid disease or age. Investigating renal cell type-specific sex hormone receptor knockouts in male and female animals will be crucial to understanding sex differences attributed to sex hormone responsiveness in various renal diseases. Similar genetic studies for known activators and repressors of sex hormone action should be pursued if initial expression and mechanistic studies imply a role in cellular responsiveness.

Effects of sex chromosomes.

Current models of sex differences can be used to distinguish the effects of factors other than sex hormones (for example, sex chromosomes) on kidney phenotypes. For example, the four core genotype (FCG) mice, in which the sex-determining region of the Y chromosome gene (*Sry*) is deleted and inserted into an autosome, enables differentiation between the effects of sex chromosomes and sex hormones[64]. Studies using FCG mice have provided evidence of sex chromosome effects on hypertension[45], endothelial function[65] and bradycardic baroreflex responses[66] that were independent of sex hormone effects. However, the FCG model has not been extensively used to distinguish sex hormone receptor effects from the genomic influence of sex chromosomes in renal diseases. Additional animal models of varying X chromosome dosage are also available, in which renal function can be studied under both physiological and pathophysiological conditions[67].

Translational research

Given the wide gaps in knowledge of sex differences in renal physiology and pathophysiology, it may seem premature to think about translational research, defined here as the process of applying basic and clinical science knowledge to address critical medical needs and improve health outcomes. However, several areas in sex difference research warrant consideration when planning future translational studies. For example, it is important to assess whether promising disease biomarkers are differentially expressed in males and females, or whether sex differences in renal responses to drug therapies exist. Another important area for consideration is the study of individuals who have undergone significant changes in hormonal status in their lifetime (for example, transgender individuals) to further explore the physiology and implications of sex on varying disease states.

Sex-specific disease biomarkers.

A growing body of literature supports the importance of sex-specific biomarkers in predicting disease progression and outcome. A lack of controlling for sex is proposed to lead to up to 40% false discoveries in biomarker studies[68] and to under-recognition of potential pathophysiology. For example, in ischaemic heart disease and heart failure, evidence suggests that ‘unisex’ troponin reference intervals might underdiagnose myocardial infarction in females, as baseline circulating concentrations of troponin are lower than in males[69]. Women with acute coronary syndromes present with lower troponin levels than men and those who do reach the standard troponin threshold might have suffered more severe myocardial damage at the time of detection than their male counterparts[69]. Another common biomarker with known sexual dimorphism is C-reactive protein, a marker of

inflammation that may be up to 60% higher, on average, in women than in men[70]. Biomarkers may not only vary with sex but also with hormonal status among women, which is influenced for example, by the use of oral contraceptives, postmenopausal hormonal changes and stage of menstrual cycle[68]. For example, excretion of urinary fructose-1,6-bisphosphatase and glutathione-S-transferase peaked in women after ovulation and the onset of menses, whereas men and postmenopausal women showed consistently low levels of urinary fructose-1,6-bisphosphatase excretion over comparable time periods[71]. Despite these observations, potential sex-based differences in biomarkers are often overlooked.

Biomarkers of kidney function and disease may also differ by sex, but this possibility has not yet been rigorously studied. Studies in rats that demonstrated sex differences in the excretion levels of traditional and novel biomarkers of nephrotoxicity (such as alkaline phosphatase, cystatin C, liver-type fatty acid-binding protein (L-FABP), γ-glutamyl transpeptidase (γGTP) and β_2-microglobulin (β_2M)) support this notion[72]. Databases of biomarkers should therefore include detailed phenotyping so that sex-based differences in body composition and kidney function can be taken into account[73]. The use of biorepository samples from well-defined cohorts with known outcomes and shared databases should be encouraged — these resources might foster collaboration between basic scientists and clinicians and aid in the formulation of valid questions about how sex affects kidney function and disease progression. Existing information platforms, such as electronic health records, or the pairing of study cohorts with the Centers for Disease Control and Prevention, the World Health Organization and renal databases (for example, the US Renal Data System; USRDS) might be used to store and connect data from various cohort studies. Finally, given the potential implications of female hormonal status, as described in cardiovascular disease, it is important to examine biomarker repositories within the context of a woman's life cycle, accounting for menopausal status[73].

Renal responses to drug therapy.

Men and women differ in their responses to drug treatment owing to physiological differences, such as body weight, height and body surface area, as well as potential differences in pharmacokinetics or pharmacodynamics[74]. Unfortunately, sex is rarely considered when prescribing the type or dose of medication for the treatment of chronic diseases. In the context of renal diseases, many questions remain unanswered.

Studies in experimental models suggest an interaction between oestrogens and the renal expression and activity of components of the renin-angiotensin system[75,76]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are recommended for the treatment of patients with diabetic and non-diabetic proteinuric renal disease, regardless of sex[77]. However, a 2019 population-based study suggested an increased hazard for the composite outcome of cardiovascular death, hospitalization for myocardial infarction or unstable angina in female (but not male) patients prescribed an ACEI compared with an ARB after a first myocardial infarction[78]. Likewise, all-cause mortality was higher in elderly women (but not men) with congestive heart failure who were prescribed ACEIs compared with ARBs[79]. These observations suggest possible sex differences in the response

to ACEIs or ARBs, but data on such differences are not commonly analysed or reported and these issues require further study.

Sex-specific differences in pharmacokinetics and pharmacodynamics have also been proposed to exist in kidney transplant recipients treated with immunosuppressive drugs. Clearance of calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors is thought to be higher in women than in men[80,81], whereas clearance of glucocorticoids and mycophenolate mofetil might be lower in women[82,83]. Of note, prolonged gastrointestinal transit time and lower gastric acid secretion might decrease the absorption of drugs in females compared with males, rendering certain medications less effective in women[84].

Another aspect to consider is the effect of sex on renal drug metabolism. Differences between the sexes in the filtration, renal tubular transport and excretion of some drugs might lead to greater toxicity in women than in men[85]. Thus, medications excreted by the kidney, either as active drugs or metabolites, might have differential effects on women and men.

New study cohorts.

The dichotomous study of outcomes in males versus females may be an oversimplification — new cohorts might elucidate the physiology and implications of sex in varying disease states. Such cohorts might include transgender individuals, body builders, patients with androgen insensitivity, individuals with infertility or who are undergoing fertility therapy, persons with genetic variations that result in sexual dimorphism and pregnant women with medical conditions. Studies in such individuals might lead to a better understanding of how sex hormones contribute to disease mechanisms independently of sex chromosomes in humans.

The differential and respective effect of genetic, hormonal and environmental factors may be explored in transgender individuals who undergo gender-affirming medical intervention with sex hormones[86]. For example, cross-sex treatment with oestrogens has been associated with a higher risk of venous thromboembolism and ischaemic stroke in transfeminine persons undergoing male-to-female transformation than in age-matched cisgender male and female controls[87].Renal metabolic and functional changes in transgender individuals have not yet been explored in detail. The Gender Dysphoria Treatment in Sweden study is creating a dataset with information on patients with gender dysphoria undergoing cross-sex hormone treatment[86] and the European Network for the Investigation of Gender Incongruence, the largest study of transgender individuals to date, includes over 2,600 participants[88]. Investigation of such cohorts might enable researchers to obtain data regarding sex, gender and selected renal parameters in the context of CKD to evaluate how physiological changes driven by exogenous hormones affect the renal phenotype.

Tools, approaches and resources

To date, the majority of renal physiology studies have been conducted in males[89]. One reason for this sex bias might be the belief that females are more intrinsically variable than males, owing to their hormonal cycles[90]. Although future studies should certainly include females, such a change would be insufficient to address the existing knowledge gap. First,

many existing experimental models of renal disease have not been adapted for females. This difference is consequential, because observations in animal models, as well as in selected human populations, demonstrate that females commonly seem to be protected, or at least develop a less severe form of the renal disease being studied[91]. This discrepancy highlights the importance of either developing new models or adapting existing models to induce a phenotype in females. Second, studying a single sex in isolation often masks important research questions that might only be answered through a direct comparison of the two sexes in adequately powered studies. Third, both preclinical and clinical studies are needed to appropriately address specific research questions concerning sex and the kidney[92]. In addition to experimental models, there seems to be a need to develop appropriate tools and approaches for studying sex differences, some of which are outlined below.

New animal models.

A study that analysed high-throughput phenotype data from 14,250 wild-type and 40,192 mutant mice (representing 2,186 knockout lines) showed that up to 56.6% of quantitative traits in wild-type mouse models exhibit a degree of sexual dimorphism[93]. These findings indicate that extrapolating data from a sample in which males are over-represented to the general population may be misleading and underscores the need to avoid the exclusive study of male animals. In the context of renal disease, the lack of animal models that adequately recapitulate the human condition, especially for women, needs to be addressed. Models of renal disease in which the female kidney is protected, including hypertension, acute kidney injury (AKI), ischaemia-reperfusion and diabetic kidney disease[94–98], represent an opportunity to investigate the mechanisms underlying resistance to renal disease in women. Such insights might contribute to the development of novel therapeutic approaches for both women and men.

Animal models in which gonadal hormones or sex hormone receptors have been manipulated, such as the aromatase-deficient mouse or the ERα- and ERβ-deficient mouse, are widely available, but have not been as extensively used by the renal research community as in other fields. Superimposing gonadal hormones and sex hormone receptor deletions on existing experimental models of renal disease might create useful tools for the study of sex differences.

As discussed above, the FCG model can be used to separate the contribution of sex hormones from the effects of sex chromosomes[64]. Moreover, studies in women with Turner's syndrome (who have a single X chromosome; XO) show that those with maternal X chromosome inheritance (XmO) have a stiffer aorta[99] and a greater atherogenic profile[100] than those with paternal X chromosome inheritance (XpO). Haploinsufficiency for genes encoded in the short arm of the X chromosome (Xp) also increases the risk of type 2 diabetes mellitus[101]. However, the importance of X inheritance and X inactivation in kidney disease has yet to be investigated. Unfortunately, the poor survival of XpO animals hinders the use of XmO and XpO mice in parallel to differentiate the effects of maternal versus paternal inheritance of the X chromosome[102]. Thus, additional animal models are needed to further evaluate the role of sex chromosome dosage, parental imprinting and escape from X-inactivation in renal physiology and pathophysiology.

Datasets from experimental models that use large animals constitute another rich resource for sex difference research. Unlike typical breeding practices in mice and rodents, in which frequently only the male pups are kept for further study, the expense of breeding large animals promotes investigations using both sexes. Collating renal data from these large animal datasets might enable comparative genomics studies between the sexes.

Existing cohorts.

The NIDDK supports several centres that can be used to promote tool development and provide necessary resources to the renal research community interested in sex differences research. For example, the O'Brien Kidney Center and Polycystic Kidney Disease Centers provide core services and funds for pilot and feasibility projects[103]. These programmes can provide an avenue for investigators to initiate studies in sex differences. The core services vary between centres but can either serve as universal phenotyping resources or provide needed reagents for the investigative community. Furthermore, the development of novel hypotheses that inform future epidemiological, clinical and basic mechanistic studies on sex differences in renal disease could be facilitated by developing data mining tools and encouraging investigators to efficiently utilize existing data from human cohorts, including data from the Chronic Renal Insufficiency Cohort study (CRIC)[104], Chronic Kidney Disease in Children Cohort study (CKiD)[105] and the USRDS[106].

The NIDDK initiated the Kidney Precision Medicine Project (KPMP) in response to recognition that advances in multi-scale interrogation of human tissue and single cells have paved the way for precision medicine in nephrology[107]. This project is aimed at collecting and analysing human kidney biopsy samples from participants with AKI and CKD to create a kidney tissue atlas, define disease subgroups and identify crucial cells, pathways and targets for novel therapies. The KPMP also creates a timely opportunity to collect sex and gender data elements on a large cohort of patients with renal disease. Specifically, it would be useful to collect data on hormonal and reproduction status, number of pregnancies, as well as psychosocial and psychological variables that affect gender identity for all consenting KPMP participants. Such a valuable dataset would not only benefit the renal community but could also serve as a blueprint for similar projects in other areas of medicine; collecting such data in all prospective cohorts should be encouraged.

Multidisciplinary research.

The future of sex differences research will require scientific partnership between the renal research community and investigators outside traditional nephrology. Contributions from endocrinologists, sex hormone receptor biologists, reproductive physiologists and geneticists will be essential to provide context and ensure appropriate interpretation of emerging data. Chemists and structural biologists must also be engaged to develop novel SERMs and selective androgen receptor modulators that enable finer experimental manipulation of sex hormone receptors. Establishing teams that include such experts will be crucial to much-needed research.

Multidisciplinary and collaborative studies should be encouraged to prospectively address issues regarding the physiology and implications of sex differences in kidney health and

disease. These research teams should include basic, clinical and statistical expertise, and use systems approaches, rather than organ-specific investigations. To foster a community of collaboration between basic and clinical scientists, the potential to increase support for specific training programmes and early career awards to develop the next generation of translational investigators (both clinicians and basic scientists) should be explored.

Conclusions

Accumulating evidence from epidemiological and clinical studies suggests that sex-related differences might exist in the prevalence, course and severity of renal diseases. Experimental studies have provided some evidence that female sex hormones might be renoprotective, but a better understanding of how sex hormones and sex chromosomes regulate renal function under both normal physiological and pathophysiological conditions is needed. The opportunities for future research outlined in this report, directed at addressing some of these knowledge gaps, also highlight the need to develop new resources and appropriate training. These opportunities are not intended to limit or direct future research related to sex differences in renal disease, but rather to stimulate thought and interest in the research community as it considers sex as a biological variable[108].

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Glossary

Parental imprinting

A process that results in allele-specific differences in transcription, DNA methylation and DNA replication timing

X chromosome mosaicism

The presence of two populations of cells in the body: some cells have two X chromosomes whereas others have only one X chromosome

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Box 1 |

Opportunities for the study of sex differences in renal disease

Clinical research

- Investigate the epidemiology of sex differences in renal diseases
- Define the effects of sex in renal disease pathophysiology
- Develop standardized core data elements and outcomes related to sex and gender in clinical studies

Basic research

- Develop resources and a knowledge portal to promote fundamental understanding of physiological differences between male and female kidneys
- Develop an atlas of hormone-responsive cells in the kidney
- Create a database of renal phenotypes in existing models of sex hormone and activator gene knockouts
- leverage existing models of sex differences to differentiate between the effects of sex hormones and those of sex chromosomes on renal physiology in preclinical models

Translational research

- Develop sex-specific biomarkers for renal diseases
- Examine sex differences in renal responses to drug therapy
- Explore new cohorts for translational studies
- Develop translational tools to study sex differences in renal disease

Tools and resources

- leverage existing animal models and develop new models
- leverage existing cohorts
- Promote multidisciplinary research

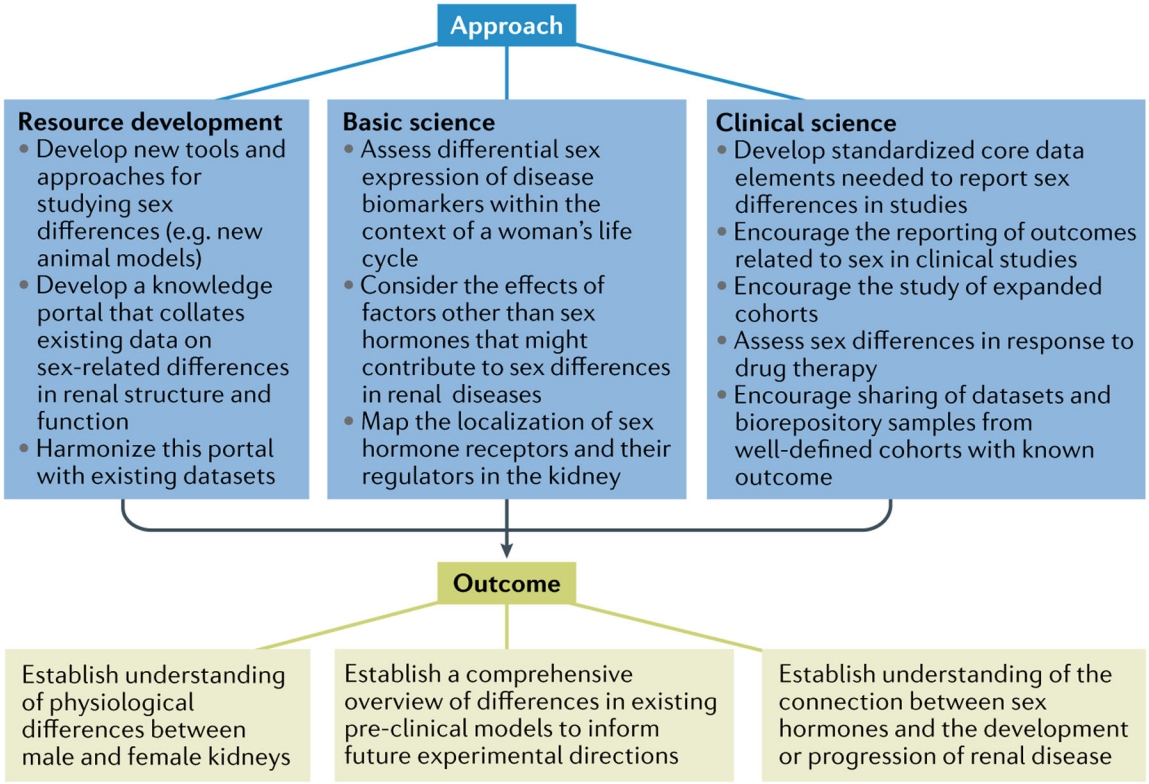

Fig. 1 |. Strategies to aid understanding of sex differences in kidney health and disease.

In recognition of the need to address controversies and knowledge gaps related to understanding the role of sex in kidney physiology and pathophysiology, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) asked leading experts in the field to discuss key considerations and identify opportunities for future research. They identified several challenges to basic and clinical science research related to sex differences, some of which could be overcome by developing new research tools and experimental models, and by expanding the availability of existing datasets for interrogation to answer relevant scientific questions around sex and gender differences that affect kidney health and disease. Improving our understanding of the complex interplay of factors that contribute to sex differences in kidney health and disease could contribute to improving the health of both women and men.

Table 1 |

Sex differences in renal structure and function in experimental models

Parameter	Sex differences	Species	Refs
Kidney size and morphology	Renal mass, size of renal cortex and proximal tubules are greater in males than in females	Mice, rat, human	46–48
Renal haemodynamics	Male kidney is vasodilated relative to the female; total vascular resistance per glomerulus is greater in females; urine protein excretion is higher in males; proximal sodium transport is lower in females	Rat, mouse	49–51,53
Sodium transport	Phosphorylation of sodium–hydrogen exchanger 3 (NHE3) is greater in females; Na^+–Pi cotransporter 2 protein expression is lower in females; abundance of total and phosphorylated Na^+/Ch^- cotransporter (NCC) and ENaC (α- and γ-subunits) is greater in females	C57BL/6 mice	53
Glucose transport	Sodium–glucose cotransporter 2 (SGLT2) protein expression is higher in females; no sex differences at the mRNA level	Wistar rat	52
Water channel	Aquaporin 1 (AQP1) protein and mRNA expression are ~80% and ~40% higher, respectively, in males than in females	Wistar rat	53,54
Organic anion transport	Solute carrier family 22 member 6 (mOat1) protein expression is higher in males; solute carrier family 22 member 8 (mOat3) protein expression is lower in males; solute carrier family 22 member 19 (mOat5) protein expression is lower in males	C57Bl/6 mice	55,56