Sex and Gender in Glomerular Disease

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Summary
There is increasing understanding that a multifaceted interplay of sex-dependent genetic and immune dysregulation underpins the development of glomerular disorders. Regional and ethnic variations in glomerular disease incidence make delineating the effects of sex and gender on disease pathophysiology more complex, but there is a marked paucity of research in this area. This review article presents a summary of the current understanding of sex and gender in glomerular disease, highlighting the broader effects of sex and gender on autoimmunity, clinical presentations, and pathophysiology of individual glomerular diseases, as well as exploring sex, gender, and glomerular disease within a wider socioenvironmental context. It is important to specifically consider the effects of sex and gender when presenting and analyzing clinical and scientific studies on glomerular disease. Failure to do so risks promoting disparities within health care provision, neglecting opportunities to identify sex-specific biomarkers, and potentially hindering the development of sex-specific therapies.
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Sex differences in developmental, physiological, and pathologic processes have been recorded for more than 150 years.[1] In human beings, sex differences exert multiple influences on disease, affecting susceptibility, presentation, outcomes, and experience. As yet, the molecular mechanisms that underlie sex differences in autoimmune and glomerular disease are not completely understood. There is, however, increasing understanding that a multifaceted interplay of sex-dependent genetic and immune regulation underpins these complex disorders.

Although the terms sex and gender often are used interchangeably, there are important differences between the two.[2] For the purpose of this review, sex will refer to characteristics that are biologically defined and assigned at birth, as according to the World Health Organization definition.[3] Gender will refer to the more socially constructed features, the "sense of self," which may not match sex assigned at birth.[3] Both sex and gender may impact significantly on health and disease: with sex potentially modulating disease progression and therapeutic responses; and gender influencing interpersonal communication, nonpharmacologic disease management, and desire or ability to access health care.[4]

This review explores why sex and gender are important in glomerulonephritis, and the impact that sex has on autoimmunity and glomerular disease, before exploring individual disorders in detail. Finally, it explores the effects of sex and gender on socioenvironmental aspects of glomerular disease.

WHY SEX AND GENDER ARE IMPORTANT IN GLOMERULAR DISEASE

It is important to examine the role of sex and gender within disease because they can influence pathophysiology, clinical outcomes, and experiences of illness (Fig. 1). This is particularly true for glomerulonephritis, for which the effects of sex on disease frequency, distribution, and severity are well recognized.[5,6] Glomerular disease as a single entity has a marked male preponderance, and males outnumber females affected in all of the primary glomerulonephritides.[5-7] Lupus nephritis is the only glomerular disease in which more females are affected,[7] although sex differences in anti–neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) may be changing as occupational and recreational exposure to environmental hazards evolve.[5] These epidemiologic variations highlight the important role that gender also plays in the development of glomerular disease. Given that sex frequencies in glomerulonephritides also differ in prevalence geographically,[8] while genetic modifiers may have key roles to account for the geo-ethnic differences, the effect of different cultures and environments on perceived sex/gender roles also should be considered.

There are many challenges to untangling the biological and nonbiological factors that influence outcomes in glomerular disease because data presented in research studies often are incomplete, and historically have

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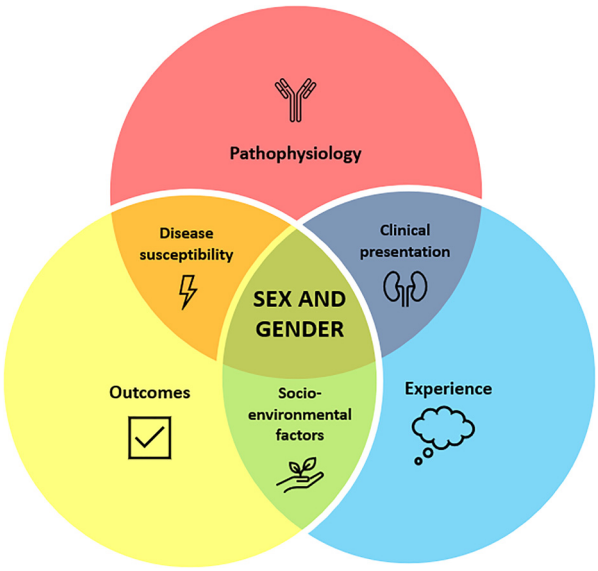

Figure 1. Influences of sex and gender on glomerular disease.

usually focused on the influence of sex and biological processes on disease pathogenesis and outcome.

In animal research, a disproportionate number of models exclusively use males, thus limiting our ability to extrapolate research findings to both sexes. For example, in a study of high-impact renal journals, for every experiment performed with female animals, there are between 5 and 16 studies conducted solely in males, a figure that disappointingly has not improved over the past decade.[9]

Similarly, effects of sex and gender often are not considered or recorded when reporting outcomes in clinical trials. Historic literature primarily will have considered sex rather than gender (even when described as the latter) and focused on biological differences or mechanisms. Alongside this, it also is rare for studies to report the menopausal status of patients, or whether there is a history of oral contraceptive or hormone therapy use among participants, yet these medications may significantly impact disease progression and severity.

It has been shown repeatedly that women have an increased incidence of chronic kidney disease (CKD), but are less likely to progress to end-stage kidney disease (ESKD).[10] There are no significant differences in the rate of progression of CKD in women compared with men, so why women are less likely to undergo renal replacement therapy has not been answered satisfactorily. Women with CKD are less likely to have seen a nephrologist, and have lower education and income levels than their male counterparts,[10] raising important questions on equity and access to health care.

Finally, negative experiences because of health care professionals failing to consider sex or gender can adversely impact clinician−patient relationships and disease trajectories. Glomerular diseases often are chronic, long-term conditions, requiring multidisciplinary care and frequent hospital attendances: damaged clinician−patient relationships can have long-lasting repercussions.

Ignoring the effects of sex and gender on glomerular disease when presenting and analyzing clinical and scientific studies risks promoting disparities within health care provision, and neglecting opportunities to identify and develop sex-specific biomarkers or therapies, which may prevent the implementation of personalized medicine in glomerulonephritis (GN) in the future.

IMPACT OF SEX ON AUTOIMMUNITY

Although diverse pathogenic processes underpin the different forms of GN, in common they share an autoimmune mechanism of kidney injury. The marked female bias in autoimmune disease is striking.[11] It is estimated that nearly 80% of those affected by autoimmune disease are women[12] and that female sex carries a risk of autoimmunity far higher than any other identified susceptibility locus from genome-wide association studies and meta-analyses.[12,13] Early work in this area focused on the influence of sex hormones, encouraged by the finding that many autoimmune diseases (particularly Th1-associated, or inflammatory autoimmune diseases such as rheumatoid arthritis or multiple sclerosis) improve significantly during pregnancy. This is particularly marked in the third trimester when estrogen and progesterone levels are at their highest.[4]

However, this is too simplistic a view because in antibody-mediated autoimmune diseases (T helper (Th) 2-associated), the effects of pregnancy are more variable, challenging the idea that sex hormones are solely responsible for sex differences in autoimmunity. Symptoms of myasthenia gravis can vary from pregnancy to pregnancy in the same women, and pregnancy can improve, worsen, or result in no change in myasthenia gravis symptoms.[14] Systemic lupus erythematosus (SLE), another antibody-mediated disease, frequently has been reported to worsen during pregnancy, although the severity of relapse is widely variable.[15]

Furthermore, sex hormones alone cannot explain the sexual dimorphism seen in autoimmune disease because a female sex bias also is observed in childhood when estrogen levels are similar in both sexes, and in postmenopausal women.[12] The presence of an additional X chromosome (or lack thereof) is another proposed driver for observed sex differences, as is the potential role of gut microbiota given the marked differences seen between male and female microbiomes. Intestinal microbiome abnormalities have been seen in most immune-mediated diseases.[16] Demonstrating a causal role for the gut microbiota has been challenging, but associations between the gut and glomerular disease have long been recognized. A genome-wide association study in IgA nephropathy (IgAN) showed that most loci associated

Table 1. Sex Hormones in Autoimmunity

Effects on Autoimmunity	Hormone	Effects
Inhibitory	Progesterone	• Reduces proinflammatory mediators (18) • Inhibits immune cell activation (18) • Promotes a shift from Th1 to Th2 type T cell responses (12)
	Androgens	• Inhibitory effects on immune cell proliferation, activation and response (26)
Variable	Estrogen	• Upregulates immune regulatory factors (20) • Dose dependent response on white blood cells (22,23,24) • At lower concentrations promotes a Th1 response, at higher concentrations promotes a Th2 shift. (12)
Stimulatory	Prolactin	• Inhibits negative selection of autoreactive B cells increasing antibody production (28)

Th1, T helper 1; Th2, T helper 2.

with IgAN also are associated with immune-mediated inflammatory bowel diseases, and maintenance of the intestinal barrier and response to gut pathogens,[17] highlighting the gut−renal connection in glomerular disease.

Sex Hormones

Sex hormones have been postulated as a contributary factor to the female sex bias seen in autoimmune diseases (Table 1). Progesterone is thought to be an important driver of the immune tolerance seen during pregnancy, reducing proinflammatory mediators and inhibiting immune cell activation.[18] Progesterone decreases activation of natural killer cells, macrophages, and dendritic cells, and promotes a shift from Th1 to Th2-type T-cell responses,[12] all of which are thought to contribute to the beneficial impacts of pregnancy on some diseases, as well as promoting maternal immune tolerance to the semi-allogenic fetus.[19]

Effects of estrogen on autoimmunity are more challenging to untangle. Estrogen levels vary across the menstrual cycle, are high during pregnancy, and decrease significantly after menopause. Estrogen receptors (ERs) are expressed in immune cells, with ERα highly expressed in T cells, and ERβ highly expressed in B cells. Estrogen has a plethora of biological effects, acting directly to up-regulate various immune regulatory factors, via ERs,[20] via estrogen response elements on target genes, and through interaction with estrogen response element−independent transcription factors in immune cells.[21] Effects of estrogens on white blood cells are dose-dependent and vary according to cell type. Estrogens increase neutrophil number, but overall inhibit their activation and migration[22]; enhance natural killer cell cytotoxicity and interferon-γ production, but down-regulate natural killer cell granzyme B secretion and cell surface activation markers[23]; enhance production of proinflammatory cytokines at low concentrations, and suppress their production at higher concentrations.[24] In summary, at lower estrogen concentrations, immunostimulatory responses promote a Th1 response, but at high concentrations, a Th2 response is stimulated.[12] To further support the role of estrogen in influencing sex differences in autoimmunity, performing oophorectomy is protective against the development of disease in lupus-prone mice.[25]

Androgens can be considered primarily anti-inflammatory mediators, exerting inhibitory effects on immune cell proliferation, activation, and responses.[26] As such, they have been shown to provide protective effects in various models of autoimmune disease.[27] In contrast, prolactin is considered immunostimulatory and increases autoantibody production by inhibiting the negative selection of autoreactive B cells.[28] Positive correlations between circulating prolactin levels and disease activity in patients with SLE have been reported, but causality has yet to be shown.[29]

Sex Chromosomes

Many genes responsible for immune function are located on the X chromosome.[18] These genes code for proteins including pattern recognition receptors (such as *TLR7* and *TLR8*), cytokine receptors (eg, *IL2RG* and *IL13RA2*), and transcriptional factors (eg, *FOXP3*).[18] Several of these show a female expression bias or are hypomethylated in female but not male patients with SLE.[12] The inherited disorder Klinefelter syndrome also highlights the importance of X dosage in autoimmunity. Klinefelter syndrome occurs when males have an additional X chromosome (karyotype XXY), causing low testosterone, increased gonadotrophins, and increased estrogen levels. Males with Klinefelter syndrome have an immune profile more similar to that of females, with higher levels of immunoglobulin, B cells, CD4+ T cells, and CD4/CD8 ratios compared with XY male controls,[18] and an increased risk of SLE.[30] Treatment with testosterone therapy reverses many of the immunologic effects seen in Klinefelter syndrome.[18] Similarly, females with Turner syndrome (karyotype XO, or those who have significant X chromosomal deletions) have lower immunoglobulin levels and T and B cells compared with XX females,[18] highlighting the importance of the X chromosome in modulating autoimmunity.

The X chromosome is enriched in microRNAs (miRNAs), transcripts that are not translated into proteins but that regulate gene expression and are essential for maintaining a balance between immune tolerance and immune response.[31] miRNAs are thought to control the development and activation of T and B cells, and are expressed differentially between the two sexes. The high density of miRNAs seen on the X chromosome means that females may express more as a result of incomplete X inactivation. In females with SLE, a subset of X-linked miRNAs were found to be overexpressed,[32] possibly contributing to the sex differences in disease susceptibility seen.

Gut Immunology and the Microbiota

The gut microbiota plays a fundamental role in the maturation and modulation of innate and adaptive immunity, and is itself shaped by the immune system.[33] Both gut immunology and microbiota show sex differences, with a trend to enhanced innate immunity and attenuated adaptive immunity in males and increased microbiota diversity in females.[34]

There is increasing evidence for a role of the gut microbiota in initiating sexually dimorphic autoimmunity. Female nonobese diabetic mice develop spontaneous autoimmune type 1 diabetes at twice the frequency of male mice, a sex difference that is removed when housing the mice under germ-free conditions. Furthermore, when male intestinal microbiota was transferred into these females, they were safeguarded against development of type 1 diabetes, signifying a protective role for the (less-diverse) male microbiome.[34] Together, animal data suggest that sex and androgens regulate gut microbiota diversity and function, which reciprocally influences the immune response and development of autoimmunity.[12]

IMPACT OF SEX AND GENDER ON GLOMERULAR DISEASE

In addition to the systemic effects of sex and gender on autoimmune disease, female sex is reported to be a protective factor in renal disease in general.[2] Animal studies have suggested that estrogens exert renoprotective effects.[35,36] Administering estrogen to male Imai rats resulted in attenuated progression of glomerular injury by significantly reducing proteinuria and glomerular sclerosis.[37] In further support, knockout of ERα protects female mice from developing nephritis, despite the presence of immune complexes, the production of proinflammatory cytokines in the kidneys, and normal humoral responses to immunization.[38] In contrast, testosterone has been shown repeatedly to exacerbate renal injury and dysfunction: as such, after castration, proteinuria in hypertensive rats was reduced by 80% and glomerular sclerosis was reversed.[39]

However, as with systemic differences, the influence of sex on glomerular disease may not be solely attributable to the influence of sex hormones, and very few studies have explored the role of sex chromosomes or sex-specific autosome gene expression in glomerulonephritides. In the context of hypertension, the limited studies that have explored these factors showed that in addition to the effects of gonadal hormones on blood pressure, X- and Y-linked genes, parental imprinting, and X chromosome mosaicism all contributed to sex differences in hypertension-associated renal injury[40]: it is likely that similar cellular and molecular mechanisms underlie sex differences in glomerular disease.

Women consistently are under-represented in randomized clinical trials, and clinical data exploring the association between biological sex and progression of glomerular disease are conflicting, representing the complex interactions between biological, cultural, and socioeconomic factors.[41] For example, using development of ESKD as a primary outcome (a common end point in nephrology studies) may be influenced by nonbiological factors such as differences in timing of dialysis initiation between men and women, and disparities in access to renal replacement therapy or transplantation. Even studies that use change in slope of estimated glomerular filtration rate to measure disease progression might not accurately capture biological differences between sexes, or psychosocial, economic, or cultural factors that are affected by gender.[10] A detailed review of pharmacokinetics and pharmacodynamics is beyond the scope of this review, but it is clear that sex differences in drug metabolism also could account for sex differences seen in treatment responses in glomerulonephritis.

In addition to effects of sex on disease pathobiology and the interpretation of clinical research outcomes, sex and gender significantly can influence perceptions of illness and quality of life. A study by the Cure Glomerulonephropathy Network (which included 1,115 adults and 478 children with glomerular disease) found that female sex correlated with reductions in health-related quality-of-life domains,[42] and the association of negative self-reported quality of life and subsequent mortality is well recognized.[43]

Moreover, sex can have significant effects on associated diseases: females with nephrotic disease are more likely to be anemic than their male counterparts,[44] and, compared with males, females have lower proteinuria in primary kidney disease and are less hypertensive, regardless of whether they have underlying CKD.[45,46] Furthermore, sex has distinct associations with cardiovascular disease, the risk of which is increased significantly in many patients with glomerular disease.[4]

Lastly, in a long-term study of childhood Henoch-Schoenlein purpura (IgA vasculitis), despite the majority

of included females having a good outcome (defined as healthy or minor urinary abnormalities only), 70% of subsequent pregnancies were complicated by hypertension, proteinuria, or both, with potential consequences for both the mother and her child(ren).[47] These are risks traditionally overlooked in many glomerular disease long-term outcome reports. It is unknown if glomerular disease in males has a similar effect on progeny.

SEX AND GENDER DIFFERENCES IN SPECIFIC GLOMERULAR DISEASES

Different glomerular diseases have distinct underlying pathophysiology, and, consequently, distinct sex and gender differences can be seen (Table 2). The following sections review individual glomerular diseases, including both primary and secondary glomerulonephropathies, with a particular focus on sex and gender differences.

IgAN

IgAN is the most common primary glomerulonephritis, and a major cause of ESKD. It is defined pathologically by IgA deposition in the glomerular mesangium, accompanied by a mesangial proliferative glomerulonephritis that varies widely in severity.[4] Although there is a clear male predominance worldwide, sex differences in prevalence differ geographically, ranging from a male to female ratio of 1.4:1 in Asians, to as high as 6:1 in Caucasians.[8]

The pathophysiology of IgAN remains uncertain, but an important hypothesis involves the development of antibodies against aberrantly glycosylated O-linked oligosaccharide(s) on the IgA1 hinge region.[4] Nakamura et al[48] measured antibody activity against synthetic hinge peptides and glycopeptides and found that antibody activity was significantly higher in females against all probes tested. They postulated that this might underlie a protective mechanism in females (to remove aberrantly glycosylated molecules), and potentially explain why the incidence of IgAN is higher in males.

Despite many studies exploring immunogenetic associations, a clear cause for susceptibility to IgAN has not yet been identified. Genome-wide association studies have highlighted strongly associated risk alleles within HLA coding regions, but these do not appear to be sex-specific. Reports have suggested that IgAN is familial in less than 10% of cases,[4,49] but the true frequency is unknown and likely under-reported because there are no reliable serologic or urinary markers for the disease. Sex-specific gene polymorphisms have been found to be associated with IgAN: the *NTN4* rs1362970 A/A and *GNG2* rs3204008 G/G genotype are associated with increased IgAN risk in males, and *PHLDB1* rs7389 G/T genotype is associated with higher risk in females.[50]

Clinical features vary between the sexes in IgAN. Documented blood pressure in males was higher, despite increased use of antihypertensive medication, but there was no difference in proteinuria between the sexes at either diagnosis or during follow-up evaluation.[51]

Table 2. Sex and Gender Differences in Specific Glomerular Diseases

Disease	Sex dominance	Details
IgA Nephropathy	Male (8)	• Increased antibody activity (and removal) against aberrantly glycosylated IgA in females (4, 48) • Gender-specific gene polymorphisms confer increased risk (49) • Higher blood pressure seen in males (50) • No gender differences in proteinuria, disease activity or outcomes (8, 50)
Membranous Nephropathy	Male (50, 55)	• Higher blood pressure and proteinuria seen in males (50) • Better prognosis in females: higher renal survival, more likely to achieve complete remission and lower relapse rate (4, 50)
Minimal Change Nephropathy and FSGS	Male (5, 50, 56, 57)	• MCN: No gender differences in clinical phenotype or remission rates (57) • FSGS: higher levels of proteinuria, increased risk of relapse and less likely to achieve remission in males (7, 50, 58) • Reduced levels of renal survival and increased risk of death in males (50, 59)
Anti- GBM disease	Equal (4, 63)	• Clinical presentation more dependent on age and smoking status than gender (64,65) • Concurrent ANCA positivity more common in females (4, 69) • No gender differences in long term renal outcomes (63)
Lupus Nephritis	Female (13)	• Increased disease activity and more aggressive histopathological findings in males (70-72) • Males less likely to achieve complete remission (73, 75) • No gender differences in long term renal outcomes or mortality (73,76,77)
ANCA associated vasculitis	Younger males and older females (79, 80)	• MPO-ANCA vasculitis associated with female sex (81) • No gender differences in clinical presentations or disease activity (84) • Conflicting long term outcome data; likely no differences between genders (80, 85-88)

ANCA, anti–neutrophil cytoplasmic antibody; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; MCN, minimal change nephropathy; MPO, myeloperoxidase.

Several studies have shown more progressive disease in males,[52] but others showed no difference.[51,53] Similarly, data examining the effect of sex on development of ESKD in IgAN are mixed, with some studies showing no differences between the sexes[8,51] and another study reporting poorer outcomes in females.[54]

Membranous Nephropathy

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in Caucasian adults and is characterized by the presence of subepithelial immune deposits on biopsy.[4] Disturbance of the podocyte structure by immune complex deposition and membrane attack complex formation results in large amounts of proteinuria.

Recent technological advances in combining laser microdissection of glomeruli and mass spectrometry of solubilized digested proteins has resulted in an explosion of putative autoantigens,[55] which has challenged the traditional classification of MN into primary MN and secondary MN forms. Some antigens [eg, Phospholipase A2 receptor (PLA2R) or thrombospondin type-1 domain-containing 7A (THSD7A)] can be associated with both primary MN or a specific cause of secondary MN (eg, lupus or cancer), and so an antigen-based classification may be considered in the future.

MN is historically male dominant, affecting twice as many males as females, but data on the incidence of MN and MN subtypes are old, limited, and predominantly from North America and Europe.[51,56] Again, differences in clinical presentation can be seen between sexes. Men have significantly higher levels of proteinuria both at presentation and during follow-up evaluation, as well as higher recorded blood pressure.[51] Females have a better prognosis in MN: they are more likely to achieve complete remission and have a lower relapse rate,[4] as well as having higher levels of renal survival.[51]

Given new understanding of disease pathogenesis, we suggest the gender distribution should be reviewed in large representative cohorts, accounting for antigen subclass. It is very conceivable that the gender prevalence may have changed, particularly because infectious precipitants of secondary MN have decreased significantly with vaccination, whereas drug exposure and lupus have increased.[55]

Minimal Change Nephropathy and Focal Segmental Glomerulosclerosis

In adults, minimal change nephropathy (MCN) and focal segmental glomerulosclerosis (FSGS) together are responsible for a third of cases of nephrotic syndrome, and both conditions can be primary or secondary.[4] Whether primary MCN and FSGS represent two different disease entities or a continuation of the same disease process continues to be debated; hence, we consider them together. Both disorders are characterized by diffuse foot process effacement on electron microscope, absent immune deposits, and a severe functional defect in glomerular permselectivity.[4]

MCN and FSGS are thought to be caused by circulating factor(s) and there is a male sex bias in both diseases.[4,51,57,58] There are no gender differences in clinical phenotype in MCN,[58] whereas men with FSGS have higher levels of proteinuria at presentation.[7] This increase in proteinuria in males continues throughout follow-up evaluation, and men with FSGS are less likely to achieve remission of the disease.[51] Although no differences in rates of achieving remission in gender in MCN have been reported, one study found there was an increased risk of early relapse in females.[58] This has not been found consistently: another study found no difference in relapse rates between the sexes.[57] In contrast, in FSGS, male gender was associated with an increased risk of relapse.[59]

We did not find studies examining sex as a variable when describing disease outcomes in adult MCN. Men with FSGS have been found to have a more rapid deterioration in renal function when presenting with high rates of proteinuria[51] and poorer renal survival compared with females.[51,60] Furthermore, male sex was associated with an increased risk of death in a small study in Nigerian patients with FSGS.[60] Recurrence of FSGS in transplants is more common in males,[61] however, males are also more likely to achieve remission of post-transplant FSGS recurrence when treated with plasma exchange.[62] Given the similar disease mechanisms underpinning adult MCN and FSGS, it is likely that there will be gender differences in outcomes for patients with MCN and this is an area worthy of further exploration.

Anti−Glomerular Basement Membrane Disease

Anti−glomerular basement membrane (GBM) disease is a rare autoimmune disease caused by autoantibodies directed against the noncollagenous C-terminal domain of the α3 chain of type IV collagen. It typically presents as a renopulmonary syndrome with rapidly progressive glomerulonephritis and alveolar hemorrhage, but can present with isolated glomerulonephritis.[4]

Historically, anti-GBM disease had a male bias (indeed, the original patient described by Goodpasture[63] was a young man), but most recent studies have shown a more equal sex distribution.[4,64] Anti-GBM disease has a bimodal age distribution, with peaks in the third decade (slight male preponderance) and in the sixth to seventh decades (no gender difference).[65] Although the exact pathophysiology of the disease is unknown, environmental factors may be important triggers for disease onset. Both cigarette smoking[66] and inhalation of hydrocarbons[67] have been implicated, exposures traditionally

more common in males. Lithotripsy may be an initiator for anti-GBM disease because extracorporeal shock wave therapy can disrupt the glomerular basement membrane and unmask epitopes,[68] and urolithiasis is another male-dominated disease,[69] which may influence the incidence of anti-GBM disease developing as a consequence.

Clinical presentation of anti-GBM disease differs by sex, age, and smoking status: young male smokers are more likely to present with both lung hemorrhage glomerulonephritis, whereas a subset of young female smokers are more likely to present with isolated lung hemorrhage and no renal involvement, which may reflect differences in anti-GBM antibody subclass between the sexes.[4] There is no reported difference in clinical features among older patients.[65] Concurrent ANCA positivity is common in anti-GBM disease and dual-positive patients are more often female.[4,70] Anti-GBM disease in the elderly appears to take a milder course,[65] and there appears to be no difference between the genders in long-term renal outcomes.[64]

Lupus Nephritis

SLE has a striking female preponderance.[13] Lupus nephritis (LN) is clinically evident in up to 75% of patients with SLE, and LN shows a similar marked female bias.[5] However, among males diagnosed with SLE, a higher proportion develop LN compared with females,[71,72] and male gender is associated with the presence of proliferative LN, a more aggressive pattern of immune-complex−mediated injury.[73]

Data are conflicting, but there is some suggestion that the clinical presentation of LN differs between males and females: photosensitivity and mouth ulcers are reportedly more common in females, whereas males have more serositis and vasculitis.[74] Along with the presence of the more aggressive histologic findings described earlier, a number of studies also have reported increased disease activity in males with LN.[74,75]

Male gender consistently is associated with failure to reach complete remission in LN,[74,76] yet despite this, no gender disparities in long-term renal survival[74,77,78] or overall mortality[78] are seen. This is surprising because achieving remission is considered integral to achieving good long-term renal outcomes in LN,[79] and, as such, one might have expected a failure to achieve complete remission resulting in worse renal survival for males.

AAV

AAV is a multisystem disease characterized by pauci-immune necrotizing inflammation of medium and small blood vessels, commonly involving the kidneys. Although historically AAV GN was thought to have a slight male preponderance,[80] it now is thought that older patients (age, >75 y) are more likely to be female,[81] particularly those with myeloperoxidase (MPO)-ANCA vasculitis.[82] Approximately 20% of AAV risk is thought to be genetic, and gender-specific genotype risks have been identified, particularly in Microscopic polyangiitis (MPA).[83,84]

There are limited data exploring differences between the sexes with respect to clinical presentations of AAV. Tampe et al[85] found no sex-specific associations between clinical characteristics or with serum or urinary parameters. They also reported that systemic disease activity does not differ between the sexes. Unfortunately, this study was from a single center, retrospective in nature, with a small number of patients, and only a short follow-up period; larger multicenter studies are needed.

Gender-related outcomes in AAV have been explored but findings are conflicting. A recent multicenter cohort study from the United Kingdom and Ireland found no gender differences in patient or renal survival, or when combining ESKD and death as a composite outcome.[86] However, this contrasts with previous work by Bjørneklett et al,[87] who found male sex is associated with greater risk of ESKD. Scott et al[86] specifically questioned whether treatment using fixed-dose regimens resulted in females receiving more treatment per kilogram than males, but, interestingly, this hypothesis was not supported. A number of studies have found a higher mortality risk in female patients,[81,88] although this also is controversial, with another study showing higher mortality in males[89] and the study from the United Kingdom and Ireland showing no difference in mortality between sexes.[86]

IMPACT OF SEX AND GENDER ON SOCIOENVIRONMENTAL ASPECTS OF GLOMERULAR DISEASE

Differences in verbal, cognitive, motor, and spatial abilities have been reported between sexes and this, combined with societal and cultural influences, may affect an individual's behavior, risk taking, and/or occupational choices. Social and environmental factors may impact these further, and combined with biological risk may influence the likelihood of an individual developing glomerular disease or their subsequent disease trajectory once diagnosed (Fig. 2).

Accessing Information and Health Care

Gender affects health care behavior across all areas of medicine,[4] with women displaying greater engagement with health care in high-income countries. A study by Carpenter et al[90] looked at 232 patients with vasculitis, and how they accessed health care information. They found gender differences in medication information sources: male patients primarily asked their spouse/

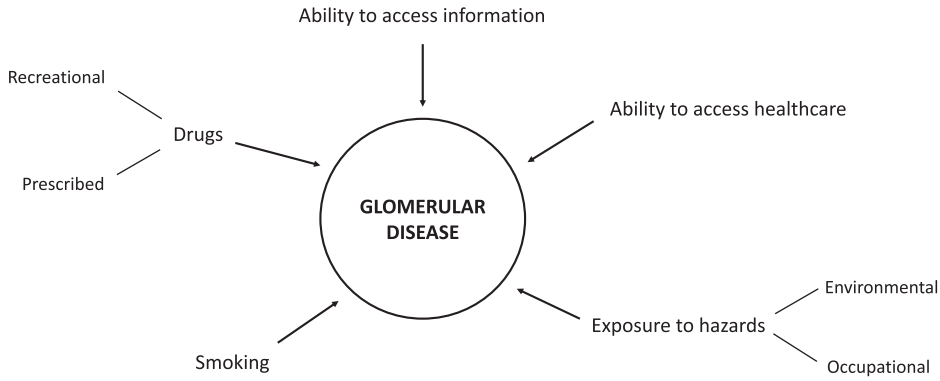

Figure 2. Impact of sex and gender on socioenvironmental aspects of glomerular disease.

partner for guidance and rated them as a more credible source than female patients did. Although females were more likely to use medication package inserts or the internet, and less likely to use nurses.

Gender differences in health care utilization also have been reported, with women showing increased health-seeking behavior.[4] This also is true within glomerular disease: males with lupus nephritis have fewer outpatient appointments and emergency department attendances compared with females.[78] Differences in health care utilization in this study had no effect on overall outcomes, making it difficult to delineate if different genders are underusing or overusing services (or, perhaps most likely, if the answer lies in between).

Gender differences in ability to access health care services also frequently have been reported. Within nephrology, it is well documented that women with kidney failure have reduced access to the transplant waiting list and to deceased donor transplantation.[91] The reasons for this are complex and might reflect disparities between outcome measures discussed earlier.[10] Serum creatinine is a commonly used indicator of kidney function but is not directly comparable between the sexes. At the same level of serum creatinine, males have better renal function than females, owing to higher average muscle mass and increased endogenous creatinine function, suggesting women might be referred for specialist care at later time points in the disease process.[41]

Exposure to Solvents and Other Occupational Hazards

Exposure to environmental and occupational hazards has long been recognized as important in disease pathogenesis for a number of autoimmune conditions. Several studies have found causal associations between organic solvent exposure and the development of glomerulonephropathies.[67,92,93] Occupations with a particularly high risk of organic solvent exposure include painters and manufacturing and chemical industries. Although men traditionally have had higher occupational exposure to hydrocarbons, a study exploring chemically induced rodent models of lupus showed gender differences in the downstream effects of exposure to organic solvents: female mice who were injected with pristane (hydrocarbon) had higher mortality rates, kidney disease, serum antinuclear and anti−double-stranded DNA antibodies than their male siblings.[94]

Exposure to silicon-containing compounds also has been associated with renal insufficiency, rapidly progressive glomerulonephritis, as well as the development of SLE, AAV, rheumatoid arthritis, and scleroderma.[95] Occupations that have a high exposure to silica dusts also often are male-predominant and include farming, mill or textile work, sandblasting, lumbar work, and drilling. Over time, occupational exposure in high-income countries appears to be improving, with a move away from manufacturing industries to service provision, and mandated improvements to health and safety legislation.[4] Working conditions for many in low- and middle-income countries remain hazardous.

Smoking

Smoking has been implicated in both the development of glomerular disease, particularly AAV,[96] but also in potentiating disease (eg, young male and female smokers have more aggressive anti-GBM disease, with marked pulmonary involvement).[4] Cigarette consumption in most countries has decreased over the past 3 decades, but despite this the absolute number of smokers has increased from 720 million people in 1980, to almost 1 billion in 2012.[97] Smoking also is associated with increased progression of CKD, so also might contribute to the excess of males with poor outcomes in glomerulonephritis.

Drugs

Many drugs are implicated in the development of AAV.[95,98] Propylthiouracil (a commonly used antithyroid medication) is well recognized, as are levamisole (often used to adulterate cocaine), hydralazine,

sulfasalazine, D-penicillamine, minocycline, and anti −tumor necrosis factor α agents. Drug-induced AAV has a more positive prognosis than primary AAV, with most patients with drug-induced AAV achieving complete remission after cessation of the disease-causing medication.[98] More females are thought to develop drug-induced AAV, largely as a result of the prevalence of thyroid disease in young women, but, interestingly, cocaine/levamisole-associated AAV also shows a female bias[99] despite cocaine use being more prevalent in males.[100]

Gender differences also have been seen with medications prescribed for glomerular disease. More females than males are prescribed medication across all illnesses, and adherence to medication is lower in women.[101] In addition, women are less likely to receive medication treatment and monitoring as recommended by clinical guidelines.[101] Although not a finding specific to nephrology, this is a particular concern in glomerular disease, given the marked toxicity of many therapeutic agents used. In addition, because of the teratogenicity of some standard treatments, females may be offered or may choose less effective treatments for their glomerulonephritis to avoid medications that impair fertility or that are contraindicated in pregnancy. The prime example of this would be the use of azathioprine for maintenance treatment of lupus nephritis instead of mycophenolate mofetil—the latter is superior in preventing relapses and improving kidney outcomes in all but Northern European White patients, but is teratogenic so females planning a pregnancy will be switched to azathioprine. Undertaking a gender-focused audit of local treatment and monitoring compliance would be an achievable goal for most renal units: using a multicenter collaborative approach would benefit the wider nephrology community.

SUMMARY AND CONCLUSIONS

The majority of glomerular diseases show a male bias, with the exception of LN, which is strongly female-predominant. Regional and ethnic variations in glomerular disease incidence make delineating effects of sex and gender on disease pathophysiology complex, but there is a marked paucity of research in this area, which needs urgent action from the nephrology community. Clinical trials must ensure adequate representation of both genders when recruiting participants, and document and acknowledge potential effects of sex or sex-specific treatments when assessing outcomes. In vivo and in vitro studies must ensure data are replicated in both male and female animals, organisms, or cells, and that appropriate reporting guidelines [eg, Animal Research: Reporting of In Vivo Experiments (ARRIVE)] are adhered to. The development of both sex-specific biomarkers and sex-specific therapeutics represent opportunities to improve and ensure equity of health care provision. However, gender differences in access to health care should be recognized, and sex and gender, as well as physician biases regarding sex and gender, must be specifically considered when presenting and analyzing clinical and scientific research in glomerular disease. There is much work to be undertaken exploring the roles of sex and gender in individual glomerular diseases, which may benefit patients and their children for generations to come.

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