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Sex Differences in Transplantation

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Abstract

Sex plays a role in the incidence and progression of a wide variety of diseases and conditions related to transplantation. Additionally, a growing body of clinical and experimental evidence suggests that sex can impact the pharmacokinetics and pharmacodynamics of several commonly used immunosuppressive and anti-infective drugs in transplant recipients. A better understanding of these sex differences will facilitate advances in individualizing treatment for patients and improve outcomes of solid organ transplantation. Here, we provide a review of sex-related differences in transplantation and highlight opportunities for future research directions.

Introduction

Sex plays a role in the incidence, prevalence, and progression of a wide variety of diseases and conditions related to transplantation. Additionally, a growing body of clinical and experimental evidence suggests that sex can impact the pharmacokinetics and pharmacodynamics of several commonly used drugs in transplant recipients. Accordingly, more attention in biomedical research is now focused on understanding the ways in which therapeutics may be tailored according to sex. In fact, the NIH has recently recognized the importance of considering sex in experimental study design and now requires sex and gender inclusion plans in preclinical research.[1] The goals of this review are to describe how sex influences allograft function, infectious complications, and the pharmacokinetics and pharmacodynamics of commonly used transplant medications.

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Impact of sex on allograft function

Prior to kidney transplantation, sex has an impact on the progression of renal disease. Males appear to have a more rapid deterioration of kidney function independent of other risk factors, such as blood pressure or protein intake. This has been observed in experimental models of renal injury as well as in clinical studies. Kang et al studied the role of estrogen on preserving renal vasculature in 5/6 nephrectomized Sprague-Dawley rats.[2] At 12 weeks, male rats had worse renal function than females, as evidenced by serum creatinine values of 2.1 +/− 0.8 mg/dL in male versus 1.4 +/− 0.6 mg/dL in females ($p<0.05$). Proteinuria was also worse in males than females (urine protein 159 +/− 45.4 mg/day in male versus 96.4 +/−20.6 in females) ($p<0.05$). These experimental results corroborate many clinical studies that illustrate that male sex is associated with a faster progression of chronic renal disease. A meta-analysis of available studies found a highly significant association between sex and nondiabetic chronic renal disease progression, in the direction of males having less favorable renal outcomes.[3] The underlying mechanisms for the sex-discrepancy in renal disease progression are unclear. Several potential mechanisms have been postulated, including differences in renal hemodynamics[4–6], the renin-angiotensin system, macrophage infiltration[7], and a protective role of estrogen[8], possibly via the stimulation of vascular endothelial growth factor (VEGF).[2]

Sex differences persist for graft outcomes following renal transplantation. A large study of 73,477 renal transplant recipients performed with data from the U.S. Transplant Scientific Registry and the U.S. Renal Data System showed a tendency for females to have more early graft loss and less late graft loss.[9] In particular, females had a 10% increased odds of acute rejection in the first 6 months after transplantation (OR=1.10, 95% CI 1.02–1.12). On the other hand, females had a 10% reduced risk of late graft loss from chronic allograft failure, defined in their study as graft loss beyond six months not attributable to death, recurrent disease, acute rejection, thrombosis, infection, noncompliance, or technical problems (RR=0.9, CI 0.85–0.96).[9] The risk for chronic allograft failure was age dependent, with younger patients (< 45 years of age) having no significant difference between the sexes in chronic graft loss. However, the risk for chronic allograft failure increases significantly with increasing age for both sexes, yet this effect was greater for males than females ($P<0.001$). For example, in women, a significant increase of the risk for chronic allograft failure was evident only beyond 65 years of age, but male recipients had a significant increase in risk beyond 45 years of age. The differences noted in this study were independent of donor factors, immunosuppressive regimen, and panel reactive antibody (PRA) levels.

Sex differences in graft survival have also been observed in pediatric transplant recipients. However, in contrast to adults, female sex is a predictive risk factor for graft failure for adolescents and children undergoing kidney transplantation. This finding was described in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) report which summarized outcomes from 1982 to 2010 in 10,632 pediatric kidney transplant patients. Male recipients had less risk compared to female patients for both living donor (HR of male sex = 0.88) and deceased donor (HR of male sex = 0.85) transplants.[10] A recent study of outcome differences between 73 pediatric transplant renal transplant recipients again found higher risk in female children as compared to males (HR of female sex = 9.0).[11]

Thus, a discrepancy exists in sex differences in transplant outcomes between adults and pediatric patients, whereby adult female recipients tend to have more early graft loss and less late graft loss, as compared to pediatric recipients where female sex is a predictive factor for late graft loss.

The underlying reasons for sex differences in the progression of renal disease and graft outcomes, including discrepancies between pediatric patients and adults, are not well understood. Considerations include hormonal regulation of the immune response and hormonal changes as a function of time, including pre-puberty and post-menopause. For instance, several studies have suggested an increased risk for acute rejection in females, attributed to the higher likelihood for preexisting anti-HLA antibodies due to pregnancy. Conversely, a lower risk of chronic graft dysfunction in adult females may be attributable to a protective effect of sex hormones such as estradiol, and this may also explain why female sex is not protective against late graft failure in pediatric patients. This hypothesis is supported by animal studies. Muller and colleagues studied the influence of testosterone and estradiol on the development of chronic rejection in an orthotopic kidney transplant model in ovariectomized female Lewis rats.[12] At 16 weeks, testosterone treated animals had more morphological alterations characteristic of chronic rejection compared to vehicle treated animals. Estradiol had a protective effect and significantly reduced the infiltration of lymphocytes and macrophages in the grafts.[12]

A separate hypothesis for the lower risk of chronic rejection in females is related to intracellular drug exposure. Cyclosporine and tacrolimus exert their pharmacological action within lymphocytes by several mechanisms including inhibition of calcineurin, inhibition of the JNK and p38 pathways, and inducing the increased expression of transforming growth factor-β1 (TGF-β1).[13] Lymphocytes also express P-glycoprotein, which can reduce intracellular drug concentrations of substrates such as cyclosporine and tacrolimus by effluxing these drugs out of the cell. Tornatore et al recently reported that females have lower expression of the gene that encodes P-glycoprotein (ABCB1) in peripheral blood mononuclear cells.[14] These data suggest that females may have reduced efflux activity of calcineurin inhibitors leading to greater intracellular drug exposure. One possibility of the reduced risk of chronic allograft failure in females, therefore, is that females have higher intracellular concentrations of calcineurin inhibitors when plasma drug concentrations are kept the same.

Pharmacokinetics of medications used in transplant recipients

Drug disposition in the body encompasses absorption from an extravascular site of administration, distribution to tissues throughout the body, and elimination by metabolism or excretion. The majority of immunosuppressive medications used in transplantation undergo metabolism by the intestine and liver, whereby biotransformation produces polar byproducts to facilitate excretion from the body. In addition, drug transporters in both the intestine and liver work in a coordinated fashion with metabolic enzymes by pumping these drugs into or out of cells. Therefore, the functional activity of intestinal and hepatic drug metabolizing enzymes and uptake and efflux transporters are principal determinants of both bioavailability, or the fraction of an administered dose that reaches the systemic circulation

unchanged, as well as the plasma concentration versus time profile, which directly relates to pharmacologic effects. The majority of immunosuppressive medications used in transplant patients exhibit a narrow range between desired pharmacologic effects and toxic effects. Meaningful sex-based differences in drug disposition pathways could result in corresponding differences in dosage requirements between men and women. Such differences may be more critical for those drugs that do not routinely undergo therapeutic drug monitoring, where dosages are adjusted to maintain trough and/or peak concentrations within a specified range.

Calcineurin Inhibitors

The calcineurin inhibitors (CNIs) tacrolimus and cyclosporine are widely used immunosuppressive drugs in transplant recipients. Following oral administration, both CNIs are metabolized by the cytochrome P450 enzyme system (CYP) located in the endoplasmic reticulum of intestinal epithelial cells. Both drugs are metabolized by CYP3A4 and CYP3A5. CYP3A4 is the predominant enzyme responsible for cyclosporine metabolism while CYP3A5 is the predominant enzyme for the metabolism of tacrolimus.[13] Both CNIs are also substrates of P-glycoprotein, a transporter localized to the apical membrane of intestinal epithelial cells, which functions as an efflux pump by moving drugs from intestinal cells back into the gut lumen. Unchanged tacrolimus and cyclosporine escaping intestinal metabolism may enter the portal vein and travel to the liver. Upon entering the hepatocytes from the sinusoidal blood, the drugs may be metabolized by hepatic CYP3A, transported back into the blood, or eliminated via biliary secretion. After entering the systemic circulation both drugs bind extensively to erythrocytes, lipoproteins, and albumin, but only unbound drug is capable of entering lymphocytes and exerting immunosuppressive effects.[13]

Both tacrolimus and cyclosporine pharmacokinetics are characterized by high intra-patient variability, which can be partially attributed to drug-interactions, food effects, diarrhea, generic substitution, and non-adherence.[13,15,16] Single nucleotide polymorphisms (SNPs) in the genes encoding for CYP3A4, CYP3A5, and P-glycoprotein also contribute to high inter-patient variability in the disposition and response to calcineurin inhibitors[17,18] which would exist independent of patient sex.

Sex-related differences in pharmacokinetics have been reported for cyclosporine and tacrolimus. A frequently cited study of 77 male and 36 female renal transplant recipients showed the weight-normalized oral clearance of cyclosporine was significantly higher in women than in men (14.8 +/0 12 mL/min/kg versus 11.4 +/− 5.93 mL/min/kg) ($p<0.05$).[19] The observation of higher weight-normalized cyclosporine clearance in females has been replicated in other studies.[20,21] This finding is in agreement with pharmacokinetic studies of tacrolimus, which again show higher clearance in females.[22] A larger analysis of 14 different CYP3A substrate drugs that are not transported by P-glycoprotein demonstrated weight normalized clearance is on average 20% to 30% higher in women than in men.[23] The mechanisms underlying the apparent differences in clearance of CYP3A substrate drugs between men and women are controversial. Paine et al studied the role of sex in modulating the intestinal content of CYP3A4, CYP3A5, and P-glycoprotein. Using duodenal biopsies

obtained by upper intestinal endoscopy from healthy men and women, no sex-related differences are seen for the expression of any of the three proteins.[24] This finding is substantiated by the observation that no sex differences exist for the oral clearance of fexofenadine, a probe for intestinal P-glycoprotein activity.[25] With respect to hepatic metabolism and transport, studies by Schmucker[26], Shimada[27], and George[28] have evaluated CYP3A protein content and function from human livers and identified no significant sex differences. Conversely, a study by Hunt showed 24% higher CYP3A activity in female liver,[29] while a study by Wolbold reported 2-fold higher CYP3A levels in females along with a consequent 50% increase in the CYP3A-dependent metabolism of verapamil.[30] Conflicting data also exists for the expression of P-glycoprotein in human liver, with one study reporting P-glycoprotein content over two-fold higher in males than in females[31], while a more recent, larger (n=94 surgical liver samples) study showed no difference in P-glycoprotein expression.[30] These inconclusive results render it difficult to ascertain a specific mechanistic basis for the observed differences in the pharmacokinetics of CYP3A and P-glycoprotein substrates such as cyclosporine and tacrolimus. As proposed by Cummins[32] and Meibohm[33], the observed sex differences may be related to differences in expression and activity of hepatic P-glycoprotein. Upon entering the hepatocytes from the sinusoidal blood, the rate of P-glycoprotein efflux from the cell may indirectly modulate hepatic CYP3A-mediated metabolism. Thus, in females, lower P-glycoprotein efflux from hepatocytes may result in higher intracellular concentrations leading to increased metabolism and ultimately increased drug clearance[32]. However, both cyclosporine and tacrolimus are primarily eliminated in the bile as CYP3A-derived metabolites and not as unchanged drug[34,35], indicating that sex differences in the expression of CYP3A are also impactful.

In summary, based upon available evidence, the weight-normalized clearance of tacrolimus and cyclosporine is higher in women than men. Nevertheless, as several other factors also contribute toward variability in the disposition of these drugs (drug-interactions, food, generic substitution, non-adherence, genetics) it is not currently feasible to put forward specific sex-based dosing recommendations. Further, with therapeutic drug monitoring, a therapeutic dose can be achieved by repeatedly obtaining blood concentrations and adjusting doses as necessary. Thus, sex differences in calcineurin inhibitor pharmacodynamics – the relationship between blood concentrations and pharmacologic effects – may be more impactful from a clinical perspective.

Mammalian target of rapamycin inhibitors

Sirolimus and its derivate everolimus are immunosuppressive drugs that inhibit the mammalian target of rapamycin (mTOR) and suppress the proliferation of T cells. Like the CNIs, both sirolimus and everolimus are substrates for CYP3A and P-glycoprotein, and thus sex differences may be expected in the direction of females having higher clearance. Accordingly, the clearance of sirolimus is 20% higher in females as compared with males,[36] which is likely related to the aforementioned sex-based differences in CYP3A and P-glycoprotein expression and activity. However, sex differences have not been identified for everolimus pharmacokinetics, as two independent population pharmacokinetic studies of

everolimus in renal transplant recipients did not identify sex as a significant covariate for clearance.[37,38]

Antimetabolites

Mycophenolic acid (MPA) is currently the most common antimetabolite used in renal transplant patients. MPA is available either as an ester prodrug (mycophenolate mofetil, MMF) or as a sodium salt (mycophenolate sodium). Following oral administration, MMF is absorbed rapidly and completely from the gastrointestinal tract and undergoes extensive presystemic de-esterification to the active metabolite MPA metabolite. MPA is primarily glucuronidated to a pharmacologically inactive glucuronide metabolite (MPAG) by UDP glucuronosyl transferases (UGT) in the intestine and liver, which is in turn transported into the bile by the multidrug resistance-associated protein 2 (MRP2) and possibly other efflux transporters that have yet to be elucidated[39]. Specific isoforms involved in MPA glucuronidation include UGT1A8 and UGT1A10 in the intestine and UGT1A9 in the liver. Using the MPAG/MPA concentration ratio as a measure of overall glucuronidation, Morissette et al studied MMF pharmacokinetics in 100 renal transplant patients.[40] The observed ratios of 14.3 ± 1.8 for men and 7.9 ± 0.4 for women were significantly different ($P < 0.0001$).[40] The nearly two-fold difference suggests a sex difference in the rate and extent of UGT-mediated glucuronidation, whereby men appear to have increased glucuronidation as compared to women. Additional studies have supported this observation. A population pharmacokinetic study of mycophenolic acid in kidney transplant recipients reported that statistically significant clinical covariates for MPA clearance included creatinine clearance, albumin concentration, sex and cyclosporine daily dose ($p < 0.001$), with males having 11% higher clearance.[41] A separate study found both sex and race differences in MPA pharmacokinetics, with male kidney transplant recipients having approximately 24% higher BMI-adjusted MPA clearance than females.[42] Theses clinical findings are corroborated by experimental evidence in rat models, in which sex differences in UGT activity have been reported[43], and in *in vitro* studies, in which men exhibited an approximately 4-fold higher level of expression of UGT2B17 than women.[44] Further, disparities in the MRP2-mediated biliary transporter of MPAG may be involved. A study by Suzuki demonstrated that the protein levels of MRP2 in the liver of male rats were significantly lower than in female rats and that the net biliary clearance of doxorubicin, an MRP2 substrate, was higher in female rats than in male rats.[45] Hormonal regulation of UGTs and MRP2 is likely implicated. It has been suggested that because estrogens are also metabolized by the UGT1A class[35], MPA could compete with the same UGT1A binding sites, resulting in reduced glucuronidation in females as compared to males[40]. In a humanized mouse model, in which the original UGT1 locus is replaced with human UGT1, *UGT1A9* expression is lower in female mice as compared to male mice, and increased in pregnant mice to 70-fold over nonpregnant values.[46] A similar ability of sex hormones to modulate expression is seen with MRP2, where the protein levels of MRP2 in female rats were lowered by treatment with testosterone so as to be similar to those in male rats.[45]

Azathioprine is another immunosuppressive antimetabolite used in transplantation. The pharmacologically active metabolite of azathioprine, 6-mercaptopurine (6-MP) is inactivated by the polymorphically expressed thiopurine S-methyltransferase (TPMT) enzyme, for

which an FDA-cleared test is available to identify patients with low TPMT activity. Studies have shown that TPMT expression is 14% higher in men as compared with women, and that testosterone increases enzyme activity.[47] However, corresponding clinical pharmacokinetic data is not available and it is unknown if the small difference in expression is clinically meaningful.

Glucocorticoids

Glucocorticosteroids are used in solid organ transplantation for induction, maintenance immunosuppression, and treatment of acute rejection. Prednisone, the most commonly administered oral formulation in the United States, undergoes hydrolysis to the active form prednisolone following absorption. Prednisolone undergoes further biotransformation by CYP3A4 and CYP3A5 to at least 10 hydroxylated metabolites, including 20β-hydroxyprednisolone and 6β-hydroxyprednisone, which are then excreted in the urine[48]

Female sex is associated with lower clearance and increased prednisolone exposure.[49–51] A study of 42 stable kidney transplant recipients compared to healthy non-transplant controls found the median dose normalized prednisolone exposure 6 hours after dose was significantly higher in females vs. males (415 vs. 297 nmolh/mg) and was increased further in women taking both estrogen and cyclosporine (median 595 nmol h/mg)[49]. Hormonal influence appears to play a role, as a separate study demonstrated that the weight-normalized unbound clearance of prednisolone was significantly lower in postmenopausal women (11.6 +/− 2.3 ml/ min/kg) compared to premenopausal women (16.6 +/− 3.5 ml/min/kg).[52] The influence of race and sex on prednisolone pharmacokinetics and pharmacodynamics has also been studied in white and black males and white and black females (n = 8 per group) after a single oral weight-adjusted dose of prednisone[50]. The study evaluated baseline and prednisone phases with 32-hour sampling in each phase. Women were studied during the luteal phase of their menstrual cycle. Total body weight-normalized free prednisolone oral clearance was higher in men vs. women regardless of race (by 22% in whites and 40% in blacks for oral clearance, $p < 0.01$). However, there were no observed sex differences in the 50% inhibitory concentration (IC50) for the effects of prednisolone on cortisol secretion. The observation that females have lower clearance of prednisone/prednisolone is in contrast to other CYP3A substrates, such as tacrolimus, cyclosporine, and sirolimus, where the opposite is observed. This finding is possibly due to higher concentrations of transcortin, a glycoprotein to which prednisolone binds, in females.[51,53–56] Prednisolone concentrations are not routinely monitored in clinical practice. Future research is necessary to ascertain whether the observed differences in prednisolone pharmacokinetics translate into differences in prednisone dosing requirements between men and women in order to optimize outcomes and minimize glucocorticoid-related adverse effects.

Influence of sex on common anti-viral agents used in transplantation

Infections are common after transplantation and some can independently affect allograft survival, including BK virus infection. Sex can impact susceptibility and clinical progression of a variety of infectious diseases, including travel-associated diseases[57], tuberculosis[58], encephalomyocarditis virus[59], and HIV[60]. The reason for the difference in susceptibility might be related to a difference in immunoreactivity, particularly humoral immunity, which

has been reported to be more robust in females as compared to males[61]. Sex-associated differences in susceptibility to infections complications in solid organ transplant recipients are not well characterized, and there is likely variability in risk factors for different infectious agents.

Male sex has been reported as a risk factor for BK virus infection.[62–64] In a retrospective biopsy-based case-control study, 79% were of kidney transplant patients with biopsy-proven polyoma virus-negative (PVN) were male as compared to 65% of case-matched PVN controls (p=0.02).[65] A separate study showed that among 880 renal transplant recipients, male gender recipient was identified as an independent risk factor for polyomavirus-associated nephropathy (HR 2.2 (95% CI 1.5 to 3.3, p<0.0001).[66] Finally, Rocha et al compared the characteristics of patients who developed BK nephritis with patients who developed acute rejection, and showed that patients with BK nephritis were more likely to be male (89 vs. 53%, p=0.04).[67] However, sex-differences in risk for BK virus in the renal transplant population are inconclusive, as some studies have showed no risk difference in one sex versus the other.[68,69]

Sex may also impact the risk for the development of CMV viremia and disease. Based on data collected from 364 solid organ transplant patients from a multicenter double blind, randomized controlled trial, female sex was significantly associated with CMV disease (Odds ratio 2.19; 95% CI 1.21, 3.99) and CMV viremia (Odds ratio 1.65; 95% CI 1.03, 2.65).[70] However, this strong association between sex and CMV has not been replicated in other studies. For example, a retrospective study of 207 renal transplant recipients evaluated risk factors for CMV infection, defined as the detection of 2 or more positive tests for pp65 antigenemia.[71] Excluding patients who did not receive CMV prophylaxis (D−/R−), donor and recipient ages and induction treatment with antithymocyte globulin were identified as risk factors to develop CMV infection, yet no significant sex-related differences were identified.[71] Separate studies have failed to show sex-related differences for CMV disease in kidney transplant patients (fever, malaise, anorexia, pulmonary, GI, hematologic, neurological, renal).[72,73] Finally, case-control studies of pneumocystic jiroveci pneumonia (PcP) in kidney transplant recipients have also failed to show any sex differences in risk.[74,75]

The reasons for possible sex-related differences in risk for BK virus and CMV are unclear and the effects of immunosuppression on differentially modulating sex-related differences in susceptibility to infectious diseases are not understood. One possibility is that gender-based differences exist in inflammatory responses to these viruses, which has been proposed to explain gender differences in prognosis for other infectious diseases.[76] Alternatively, sex may correlate with other risk factors, such as intensity of immunosuppression, ischemia reperfusion injury, HLA mismatch, diabetes, and deceased donor recipients. For CMV, a possible mechanistic explanation comes from molecular data suggesting that estradiol promotes the efficiency of transgene delivery from plasmids constructed with CMV.[70,77]

Transplant recipients routinely receive anti-infective prophylactic drugs, particularly in the early post-transplant period. Valgancyclovir, the orally available prodrug of ganciclovir, is the prophylactic drug of choice for CMV infection in moderate or high-risk transplant patients and is also used in the treatment of CMV disease. Following oral administration,

valganciclovir is rapidly and completely converted to ganciclovir, the active moiety, by intestinal and hepatic esterases. Ganciclovir is eliminated primarily in the urine, with about 90% excreted unchanged by a combination of glomerular filtration and tubular secretion. Active tubular secretion of ganciclovir is mediated by the organic anion transporter 1 (OAT1), an efflux transporter localized to the basolateral membrane of renal proximal tubule cells. Using a population pharmacokinetic approach, Perrottet et al showed females have a 24% higher ganciclovir clearance after correcting for individual body surface area and estimated glomerular filtration rate.[78] This difference potentially suggests higher OAT1 activity in female renal transplant recipients as compared to males. However, a compelling body of experimental evidence strongly suggests androgen-dependent sex differences of OAT1 function favors males over females. The rate of transport *in vivo* of the prototypical OAT 1 substrate p-aminohippuric acid (PAH) is greater in male kidneys than in female kidneys, which is in line with the finding that OAT1 protein in female basolateral membrane vesicles from rat kidney cortex is present at 40% of the level found in male rats.[79] Further, the protein abundance of OAT1 in rat cortex is reduced by castration in males, after which treatment with testosterone or estradiol results in restoration or further depression, respectively.[80] Further research is necessary to identify the reasons discrepant clinical and experimental results in OAT1 activity between male and female transplant recipients.

Future implications for patient care and clinical research

Sex influences the pharmacokinetics and pharmacodynamics of a variety of medications prescribed in transplant recipients. Concern for differences in drug efficacy and toxicity have led regulatory bodies, including the National Institutes of Health, to call for the inclusion of sex in clinical trial design,. The importance of attention to the patient's sex in common drug prescription was recently highlighted in findings from the Women's Health study where it was shown that low-dose aspirin was ineffective or harmful in women under age 65.[81]. Several other studies have addressed the role of sex in medications used for transplantation and, indeed, as noted in this review significant differences in drug clearance have been attributed to differences in the pharmacokinetics of CYP3A and P-glycoprotein substrates such as cyclosporine, tacrolimus and sirolimus between males and females. A sex difference has also been noted in the rate and extent of UGT-mediated glucuronidation, whereby males appear to have increased glucuronidation as compared to females, thus impacting mycophenolate dosing. Azathioprine is also affected by sex, as studies have shown that the enzyme that inactivates 6-mercaptopurine is higher in males than females, suggesting that lower doses might be needed in females. Likewise female sex is associated with lower clearance and increased prednisolone exposure. Sex differences in the disposition of immunosuppressive medications and implications for patient care and clinical research are summarized in Table 2.

The differences in pharmacokinetics and pharmacodynamics of commonly used medications in transplant recipients strongly point to the need to consider sex in immunosuppressive medication dosing. For those drugs that undergo TDM, there may be less need to consider a patient's sex since a therapeutic dose may be identified by trial-and-error, although incorporating sex into dosing may allow clinicians to arrive at a therapeutic dose faster. On the other hand, for drugs that are not routinely monitored, such as azathioprine, prednisone,

and mycophenolate, sex differences in drug disposition could be accounted for by adjusting doses for men and women. However, additional research is needed to elucidate the mechanistic basis for differences as well as whether sex-based dosing may yield clinical benefit. Overall, a better understanding of the role of sex as a modifier of drug exposure will facilitate advances in individualizing treatment for transplant recipients and will likely improve outcomes of solid organ transplantation.

Abbreciations

VEGF	Vascular endothelial growth factor
PRA	panel reactive antibody
CNIs	calcineurin inhibitors
CYP	cytochrome p450
mTOR	mammalian target of rapamycin
MPA	mycophenolic acid
UGT	UDP glucuronosyl transferases
MRP2	multidrug resistance-associated protein 2
6-MP	6-mercaptopurine
TPMT	S-methyltransferase
OAT1	organic anion transporter 1

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Table 1

Sex differences in drug metabolism and transport

Pathway	Transplant-related drug substrates	Sex-specific activity	Comments	References
Metabolic enzymes				
CYP3A	Cyclosporine,tacrolimus, sirolimus, everolimus, prednisone	F>M or M=F		2–5, 7–10, 11–14
UDP-glucuronosyltransferases	Mycophenolic acid	M>F	Sex differences limited to specific isozymes Hormonal regulation may be involved	20–22
TPMT	Azathioprine	M >F	Clinical pharmacokinetic data unavailable	26
Transporters				
P-glycoprotein	Cyclosporine,tacrolimus, sirolimus, everolimus	M=F (intestinal) M>F or M=F (hepatic)	Conflicting data on sex differences in the expression of P-glycoprotein in human liver	23
MRP2	Mycophenolic acid	F>M	Based on animal data. Hormonal regulation may be involved.	23
OAT1	Ganciclovir, valganciclovir	F > M (limited clinical data) M < F (animal data)		27–29

Table 2

Implications for patient care and clinical research

Immunosupressive Drug(s)	Implications of sex differences for clinical practice
Tacrolimus, cyclosporine, sirolimus	Metabolized by CYP3A with weight-normalized clearance higher in women than men; Routinely undergo TDM, thus limited utility to consider patient's sex in dosing because a therapeutic dose may be identified by trial-and-error; However, incorporating sex into dosing algorithms may allow clinicians to arrive at a therapeutic dose faster.
Azathioprine	Metabolized by TPMT which has higher hepatic expression in men as compared to women, and testosterone increases activity; Research is necessary to determine whether this difference translates into pharmacokinetic differences and whether higher doses in men would improve outcomes.
Mycophenolic acid	Undergoes glucuronidation by a variety of hepatic UGT enzymes and is also transported into bile by MRP2; Clearance is higher in men than in women; Research is necessary to determine whether higher doses in men would improve outcomes.