

Gender Mainstreaming and Transplant Surgery

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Keywords

Gender medicine · Transplant surgery ·
Liver transplantation · Kidney transplantation ·
Pancreas transplantation

Summary

Background: Gender differences in medicine are gaining in importance. In transplant surgery, not only the patient's gender but also that of the donor play an important role in the outcome of transplantation due to socio-cultural and genetic factors. **Methods:** This review article gives an overview of the latest investigations into gender-related influences in the field of visceral transplantation. For this purpose, a systematic review of the literature was performed. **Results:** In general, women are less often evaluated for and subjected to transplantation worldwide. Significantly poorer outcome can be observed in women with liver transplantation following hepatitis C cirrhosis. Furthermore, female renal grafts are less favorable in terms of outcome and survival. Gender disparities affect transplant medicine due to subtle gender-specific immunological factors. Sociocultural factors also lead to differences in the clinical treatment of men and women, which may influence overall survival. **Conclusion:** For a better understanding of gender-specific differences in transplant medicine and a possible improvement in outcome, further research in this field is necessary.

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Introduction

The influence of gender has been a concern in transplant medicine for a long time. Gender-related medicine involves individual reactions of men and women to clinical treatment based on immunological and hormonal disparities. Preconditions are different for men and women when it comes to transplantation. Statistically, women are less likely to be evaluated for transplantation [1, 2]. The prevalence of diseases for which transplantation may be indicated is not equally distributed among men and women, and immunological reactivity is highly gender-specific [1, 3]. However, outcome and graft survival are not only dependent on the recipient's sex. For example, many studies investigating donor gender have demonstrated better survival following kidney transplantation with male grafts [4–6].

While there is evidence for varying gender-specific infection rates in general abdominal surgery, in transplant surgery gender-related differences in surgical complications after kidney transplantation could not be observed [6, 7]. This article will give an overview of gender-related differences in liver, kidney, and pancreas transplantation.

Gender Disparity in Recipients

The U.S. Organ Procurement and Transplantation Network (OPTN) reported a higher percentage of men on kidney (59.3%), liver (62%), single pancreas (56.3%), and combined pancreas (54.1%) waiting lists [8]. Looking at actual transplantations, 65% of renal recipients were male as were 57% of recipients of living donor liver transplantation (LDLT) and two-thirds of recipients of living donor kidney transplantation (LDKT) [4, 8, 9]. The disparity observed between the sexes in transplantation is influenced by many factors. First, the epidemiology of diseases leading to transplantation is not equal for men and women. The most frequent indications for

liver transplantation are alcohol- and hepatitis C-induced liver cirrhosis, which are both more frequently observed in men [10]. Furthermore, male patients suffer more often from end-stage renal disease [4, 11]. Second, genetically determined immunological differences play a role. Overall, women have stronger immunological reactivity, which might exclude them from receiving a kidney transplant [1, 3]. 53% of women have preformed lymphocytotoxic antibodies against 50% of random lymphocyte donors (vs. 32% of men; $p < 0.01$), while 28% of women and 13% of men have antibodies against random donors ($p < 0.01$) [1, 12]. Third, simple anatomic preconditions can cause a size mismatch of recipient and graft, excluding small females as recipients for large grafts [2, 13, 14]. Furthermore, the size of the recipient overall may cause a bias in the allocation process. The model of end-stage liver disease (MELD) has been used for allocation of grafts since 2002/2003. The MELD score is calculated based on the latest values of bilirubin, creatinine, and international normalized ratio (INR). Due to their lower body weight and muscle mass, women have a lower creatinine and MELD score compared to men presenting with equal renal function [13, 15]. Studies have shown that 22.4% of women versus 21.9% of men died on waiting lists before the implementation of MELD, compared to 23.7% of women versus 21.4% of men dying waiting for a new organ after allocation based on MELD [15, 16].

However, there are also sociocultural reasons for women being underrepresented as recipients for organ transplantation. Women are less individualistic and particularly retain responsibility for their families. Therefore, they rarely plead their own medical concerns, which leads to a less aggressive evaluation for transplantation by healthcare providers [1].

Gender Disparity in Donors

The annual report of Eurotransplant showed a total of 1,117 male and 924 female organ donors in Europe in 2014 [17]. In general, more potential post mortem donors after cardiovascular deaths and motor vehicle accidents are male; however, both male and elderly people are most likely to refuse becoming an organ donor [18, 19]. Two-thirds of all living kidney donors are female [4, 9], and 36% of wives but only 6.5% of suitable husbands donate their kidney [4, 20]. In contrast, in LDLT, more male donors (53%) were observed up until 2010 [9]. Reasons for gender disparity in LDKT and LDLT are that a split liver from a female donor delivers too small a liver volume for successful transplantation [9]. It is assumed that women consent more often to kidney donation due to social responsibility and altruism, and because they are more likely to give in to subtle pressure [4, 21].

Liver Transplantation

More men than women suffer from chronic liver disease mostly because of the epidemiology of alcohol-induced liver cirrhosis and hepatitis C infections [4, 15, 22]. Hepatitis B-induced cirrhosis is

also more common in men, but acute liver failure due to a fulminant hepatitis B infection affects more women [15, 23]. Women suffer more frequently from autoimmune hepatitis and nonalcoholic steatohepatitis compared to men who present a more severe course of disease [4, 15, 24–28]. Primary biliary cirrhosis is strongly related to female gender (10:1), while primary sclerosing cholangitis affects more men. Hepatocellular carcinoma is usually more common in men [15, 29]. In children, more girls are affected by biliary atresia leading to transplantation than boys [4, 30]. In general, men suffering from liver disease have a higher mortality (65%) compared to women (35%) [15, 31]. Contrarily, women listed for liver transplantation have a higher mortality compared to men with the same MELD score [32]. In 2012, only one-third of liver graft recipients were female [8]. Current data determines a greater 90-day mortality for women with high MELD scores in Germany; in contrast, some studies showed a better outcome for female patients overall [8, 15, 33, 34]. It is suspected that women are allocated for smaller and older organs associated with worse graft function, which does not affect survival [15, 35]. In conclusion, the outcome for both sexes after transplantation is equal for all indications except hepatitis C-induced cirrhosis [4, 15, 28, 36–43]. Women undergoing transplantation because of a hepatitis C-induced cirrhosis have a higher risk for graft loss and rejection and a worse outcome in the case of a recurrent hepatitis C infection [8, 15, 44–46]. The donor's gender does not affect survival or outcome after liver transplantation [4, 47]. Some older studies proposed that female livers have a lower survival and that a gender mismatch leads to higher graft failure; however, more recent studies could not support the assumed outcome differences related to donor gender [4, 15, 33, 35, 47–52]. During follow-up, no gender-related differences are being observed in the incidence of malignancies or rejections; however, more women develop renal dysfunction after liver transplantation [15, 23, 50–55].

Renal Transplantation

More men than women develop end-stage renal disease requiring dialysis [4, 11, 24]. Reasons range from the effect of sex hormones on cytokine levels, growth factors, and oxidation resulting in higher intraglomerular pressures, as well as increased reactivity to angiotensin [4, 11]. Furthermore, men have a higher mortality risk on dialysis than women, possibly caused by estradiol-mediated suppression of mesangial cell proliferation [4, 56, 57]. All in all, men are more likely to receive a cadaveric kidney graft; in the United States 61.2% of available kidney grafts were allocated to male patients [1, 8]. Renal function after transplantation seems to be unaffected by the recipient's gender [58]. After renal transplantation, cardiovascular mortality in both genders is fairly similar; however, in the context of transplantation, vascular access infections and urinary tract infections are mostly seen in women [4, 59, 60]. In contrast to liver transplantation, there is a gender-related disparity in organ function, as male renal allografts generally have better function than female allografts [4–6]. Patients' survival was

higher with a male kidney graft in men 48.4 ± 0.4 years and women 46.9 ± 0.6 years ($p = 0.0020$) compared to female grafts in men 46.5 ± 0.3 years and women 42.1 ± 0.5 years ($p < 0.0001$) [4, 47]. Serum creatinine was higher in recipients of female grafts 1 year after transplantation, and male recipients of a female graft had a higher risk of rejection [4, 47]. Analysis of HLA-identical siblings showed that immunological differences and sex hormones probably influence the outcome after kidney transplantation, as the long-term outcome is superior in male donors [4, 47]. An explanation for the better function of male grafts might be their greater organ mass with a larger amount of nephrons; however, evidence is lacking [4].

Pancreas Transplantation

Data on gender disparities concerning pancreas or simultaneous pancreas-kidney transplantation (SPKT) is rare. More men (61.2%) than women underwent pancreas transplantation in 2012 [8]. Women had a greater risk for early graft failure compared to men after SPKT, caused by thrombosis and acute rejection at an earlier point in time. However, interestingly, the overall survival of pancreas grafts in women was similar to that in men [61, 62]. Female recipients of male grafts currently have the best long-term outcome for renal and pancreatic graft function [62].

Conclusion

Gender disparity influences transplant medicine in many different ways. Diseases leading to transplantation, such as alcohol- and hepatitis-induced liver cirrhosis, as well as end-stage renal disease occur more often in men. Due to this circumstance as well as genetic and anatomic preconditions and sociocultural reasons, female patients are less frequently evaluated and allocated for organ transplantation. With regard to recipient gender, long-term outcomes in liver, kidney, and pancreas transplantation are statistically indifferent. While donor gender does not play a role in liver transplantation, male renal grafts show superior function. Further investigations are necessary to unravel underlying mechanisms especially on the immunological and humoral level in order to understand the complex relationships encountered in gender medicine [63].

Disclosure Statement

The author and all co-authors disclosed any sponsorship or funding arrangements related to the presented research and review. All authors disclose any possible conflict of interest.

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