Gender Mainstreaming and Transplant Surgery

Eva Maria Teegen^a Isabell Krebs^b Corinna Langelotz^b Johann Pratschke^{a, b} Beate Rau^b

^aDepartment of General, Visceral and Transplant Surgery, Campus Virchow, Charité – Universitätsmedizin Berlin, Berlin, Germany;

^bDepartment of General, Visceral, Vascular and Thoracic Surgery, Campus Mitte, Charité – Universitätsmedizin Berlin, Berlin, Germany

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.

© 2016 S. Karger GmbH, Freiburg

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 LDLT 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.

References

- Jindal RM, Ryan JJ, Sajjad I, Murthy MH, Baines LS: Kidney transplantation and gender disparity. *Am J Nephrol* 2005;25:474–483.
- Oloruntoba OO, Moylan CA: Gender-based disparities in access to and outcomes of liver transplantation. *World J Hepatol* 2015;7:460–467.
- Yuge J, Cecka JM: Sex and age effects in renal transplantation. *Clin Transplant* 1991;257–267.
- Ceste M: Gender issues in transplantation. *Anesth Analg* 2008;107:232–238.
- Ben Hamida F, Ben Abdallah T, Abdelmoula M, Mejri H, Goucha R, Abderrahim E, el Younsi F, Hedri H, Ben Moussa F, Kheder MA, Ben Maiz H: Impact of donor/recipient gender, age and HLA matching on graft survival following living-related renal transplantation. *Transplant Proc* 1999;31:3338–3339.
- Kouli F, Morrell CH, LE Ratner LE, Kraus ES: Impact of donor/recipient traits independent of rejection on long-term renal function. *Am J Kidney Dis* 2001;37:356–365.
- Farr A, Györi G, Mühlbacher F, Husslein P, Böhmig GA, Margreiter M: Gender has no influence on VUR rates after renal transplantation. *Transpl Int* 2014;27:1152–1158.
- Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR): OPTN/SRTR 2012 Annual Data Report. Rockville, MD, Department of Health and Human Services, Health Resources and Services Administration, 2014.
- Hermann HC, Klapp BF, Danzer G, Papachristou C: Gender-specific differences associated with living donor liver transplantation: a review study. *Liver Transpl* 2010;16:375–386.
- Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, Moussalli J, Thabut D, Buffet C, Poynard D: Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. *Hepatology* 2004;40:1426–1433.
- Reyes D, Kew SQ, Kimmel PL: Gender differences in hypertension and kidney disease. *Med Clin N Am* 2005;89:613–630.
- Kjellstrand CM: Age, sex, and race inequality in renal transplantation. *Arch Intern Med* 1988;148:1305–1309.
- Axelrod DA, Pomfret FK: Race and sex disparities in liver transplantation: progress toward achieving equal access? *JAMA* 2008;300:2425–2426.
- Mindikoglu AL, Regev A, Seliger SL, Magder LS: Gender disparity in liver transplant waiting-list mortality: the importance of kidney function. *Liver Transpl* 2010;16:1147–1157.
- Heise M, Lang H: Gender-specific differences in liver transplantation (Article in German). *Zentralbl Chir* 2015;140:279–284.
- Moylan CA, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ: Disparities in liver transplantation before and after introduction of the MELD score. *JAMA* 2008;300:2371–2378.
- Undine S (ed): Eurotransplant International Foundation – Annual Report 2014. Leiden, Eurotransplant International Foundation, 2014. www.eurotransplant.org/cms/mediaobject.php?file=ar_2014.pdf.
- Barnieh L, Baxter D, Boiteau P, Manns B, Doig C: Benchmarking performance in organ donation programs: dependence on demographics and mortality rates. *Can J Anesth* 2006;53:727–731.
- Uhlig CE, Böhringer D, Hirschfeld G, Seitz B, Schmidt H: Attitudes concerning postmortem organ donation: a multicenter survey in various German cohorts. *Ann Transplant* 2015;20:614–621.
- Zimmermann D, Donnelly S, Miller J, Stewart D, Albert SE: Gender disparity in living renal transplant donation. *Am J Kidney* 2000;36:534–540.
- Biller-Adorno N: Gender imbalance in living organ donation. *Med Health Care Philos* 2002;5:199–204.
- Becker U, Dies A, Sørensen TI, Grønbaek M, Borch-Johnsen K, Müller CF, Schnohr P, Jensen G: Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology* 1996;23:1025–1029.
- Rifai K, Hadem J, Wiegand J, Potthoff A, Pieschke S, Klempnauer J, Strassburg C, Wedemeyer H, Manns MP, Tillmann HL: Gender differences in patient receiving liver transplantation for viral hepatitis. *Z Gastroenterol* 2012;50:760–765.
- Kim WR, Brown RS Jr, Terrault NA, El-Serag H: Burden of liver disease in the United States: summary of a workshop. *Hepatology* 2002;36:227–242.
- Park CW, Tsai NT, Wong LL: Implications of worse renal dysfunction and medical comorbidities in patients with NASH undergoing liver transplant evaluation: impact on MELD and more. *Clin Transplant* 2011;25:E606–611.
- Wang X, Li J, Riaz DR, Shi G, Liu C, Dai Y: Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014;12:394–402.e1.

- 27 Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM: American Association for the Study of Liver Disease: Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51:2193–2213.
- 28 Grønbaek L, Vilstrup H, Jepsen P: Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. *J Hepatol* 2014;60:612–617.
- 29 Cauble S, Abbas A, Balart L, Bazzano L, Medvedev S, Shores N: United States women receive more curative treatment for hepatocellular carcinoma than men. *Dig Dis Sci* 2013;58:2817–2825.
- 30 Balistreri W, Grand R, Suchy F, Ryckman F, Perlmutter D, Sokol R: Biliary atresia: summary of a symposium. *Hepatology* 1996;23:1682–1692.
- 31 Gesundheitsberichterstattung des Bundes 2013. www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Todesursachen/Todesursachen2120400137004?__blob=publicationFile&search=%22Sterbef%E4lle,%20Gestorbene%22.
- 32 Lai JC, Terrault NA, Vittinghoff E, Biggins SW: Height contributes to the gender differences in wait-list mortality under the MELD-based liver allocation system. *Am J Transplant* 2010;10:2658–2664.
- 33 Schoening WN, Buescher N, Rademacher S, Andreou A, Kuehn S, Neuhaus R, Guckelberger O, Puhl G, Seehofer D, Neuhaus P: Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. *Am J Transplant* 2013;13:2384–2394.
- 34 Bruns H, Lozanovski VJ, Schultze D, Hillebrand N, Hinz U, Büchler MW, Schemmer P: Prediction of postoperative mortality in liver transplantation in the era of MELD-based liver allocation: a multivariate analysis. *PLoS One* 2014;6;9:e98782.
- 35 Marthur AK, Schaubel DE, Zhang H, Guidinger MK, Merion RM: Disparities in liver transplantation: the association between donor quality and recipient race/ethnicity and sex. *Transplantation* 2014;27;97:862–869.
- 36 DiMartini A, Day N, Dew MA, Javed L, Fitzgerald MG, Jain A, Fung JJ, Fontes P: Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. *Liver Transpl* 2006;12: 813–820.
- 37 Pfitzmann R, Benschmidt B, Langrehr JM, Schumacher G, Neuhaus R, Neuhaus P: Trends and experiences in liver retransplantation over 15 years. *Liver Transpl* 2007;13:248–257.
- 38 Pfitzmann R, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nüssler NC: Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2007;13:197–205.
- 39 Kaplan MM, Gershwin ME: Primary biliary cirrhosis in men. *N Engl J Med* 2005;353:1261–1273.
- 40 Kim WR, Lindor KD, Locke GR 3rd, Therneau TM, Homburger HA, Batts KP, Yawn BP, Petz JL, Melton LJ 3rd, Dickson ER: Epidemiology and natural history of primary biliary cirrhosis in a US community. *Gastroenterology* 2000;119:1631–1636.
- 41 Singh S, Talwalkar JA: Primary sclerosing cholangitis, diagnosis, prognosis and management. *Clin Gastroenterol Hepatol* 2013;11:898–907.
- 42 Toy E, Balasubramanian S, Selmi C, Li CS, Bowlus CL: The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population. *BMC Gastroenterol* 2011;11:83.
- 43 Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, van Nieuwkerk KM, Drenth JP, Witterman BJ, Tuynman HA, Naber AH, Kingma PJ, van Buuren HR, van Hoek B, Vleggaar FP, van Geloven N, Beuers U, Ponsioen CY: EpiPSCB Study Group: Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013;58:2045–2055.
- 44 Villa E, Vukotic R, Camma C, Petta S, Di Leo A, Gitto S, Turola E, Karapantou A, Losi L, Bernabucci V, Cenci A, Tagliavini S, Baraldi E, De Maria N, Gelmini R, Bertolini E, Rendina M, Francavilla A: Reproductive status is associated with the severity of fibrosis in women with hepatitis C. *PLoS One* 2012; 7:e44624.
- 45 Lai JC, Verna EC, Brown RS, O'Leary JG, Trotter JF, Forman LM, Duman JD, Foster RG, Stravitz RT, Terrault NA; Consortium to Study Health Outcomes in HCV Liver Transplant Recipients (CRUSH-C): Hepatitis C virus-infected women have a higher risk of advanced fibrosis and graft loss after liver transplantation than men. *Hepatology* 2011;54:418–424.
- 46 Belli LS, Burroughs AK, Burra P, et al: Liver transplantation for HCV cirrhosis: improved survival in recent years and increased severity of recurrent disease in female recipients: results of a long term retrospective study. *Liver Transpl* 2007;13:733–740.
- 47 Zeier M, Dohler B, Opelz G, Ritz E: The effect of donor gender on graft survival. *J Am Soc Nephrol* 2002;13: 2570–2576.
- 48 Brooks BK, Levy MF, Jennings LW, Abbasoglu O, Vodapally M, Golstein RM, Husberg BS, Gonwa TA, Klintmalm GB: Influence of donor and recipient gender on the outcome of liver transplantation. *Transplantation* 1996;62:1784–1787.
- 49 Rustgi VK, Marino G, Halpern MT, Johnson LB, Umana WO, Tolleris C: Role of gender and race mismatch and graft failure in patients undergoing liver transplantation. *Liver Transplant* 2002;8:514–516.
- 50 McTaggart RA, Terrault NA, Vardanian AJ, Bostrom A, Feng S: Hepatitis C etiology of liver disease is strongly associated with early acute rejection following liver transplantation. *Liver Transpl* 2004;10:975–985.
- 51 Thuraijah PH, Carbone M, Bridgestock H, Thomas P, Hebbbar S, Gunson BK, Shah T, Neuberger J: Late acute liver allograft rejection; a study of its natural history and graft survival in the current era. *Transplantation* 2013;95:955–959.
- 52 Grande L, Rull A, Rimola A, Manyalic M, Cabrer C, Garcia-Valdecasas JC, Nevasa M, Fuster J, Lacy AM, González FX, López-Boado MA, Visa J: Impact of donor gender on graft survival after liver transplantation. *Transplant Proc* 1997;29:3373–3374.
- 53 Adami J, Gäbel H, Lindelöf B, Ekström K, Rydh B, Glimelius B, Ekblom A, Adami HO, Granath F: Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cancer* 2003;89:1221–1227.
- 54 Baccarani U, Piselli P, Serraino D, Adani GL, Lorenzin D, Gambato M, Buda A, Zanus G, Vitale A, De Paoli A, Cimaglia C, Bresadola V, Toniutto P, Risaliti A, Cillo U, Bresadola F, Burra P: Comparison of de novo tumours after liver transplantation with incidence rates from Italian cancer registries. *Dig Liver Dis* 2010; 42:55–60.
- 55 Fussner LA, Charlton MR, Heimbach JK, Fan C, Dirckising R, Coss E, Watt KD: The impact of gender and NASH on chronic kidney disease before and after liver transplantation. *Liver Int* 2013;34:1259–1266.
- 56 Lindeman RD, Tobin J, Shock NW: Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985;33:278–285.
- 57 Dubey RK, Gillespie DG, Keller PJ, Imthurn B, Zacharia LC, Jackson EK: Role of methoxyestradiols in the growth inhibitory effects of estradiol on human glomerular mesangial cells. *Hypertension* 2002;39:418–424.
- 58 Ayaz S, Gençoglu EA, Moray G, Gözükar MY, Haberal M: Evaluation of the effects of recipient/donor gender on early/late postoperative renal graft functions by renal scintigraphy. *Exp Clin Transplant* 2014;12: 510–514.
- 59 Dharmidharka VR, Agodoa LY, Abbott KC: Risk factors for hospitalization for bacterial or viral infection in renal transplant recipients – an analysis of USRDS data. *Am J Transplant* 2007;7:653–656.
- 60 Oien CM, Reisaeter AV, Os I, Jardine A, Fellstrom B, Holdaas H: Gender-associated risk factors for cardiac end points and total mortality after renal transplantation – post hoc analysis of the ALERT study. *Clin Transplant* 2006;20:374–382.
- 61 Colling C, Stevens RB, Lyden E, Lane J, Mack-Shipman L, Wrenshall L, Larsen J: Greater early pancreas graft loss in women compared with men after simultaneous pancreas-kidney transplantation. *Clin Transplant* 2005; 19:158–161.
- 62 Schäffer M, Bartmann V, Wunsch A, Traska T, Schenker P, Michalski S, Viebahn R: Kombinierte Nieren-Pankreas-Transplantation. *Chirurg* 2007;78:928–935.
- 63 Rau B, Riphaus A: Gender-specific aspects in gastrointestinal medicine and surgery. *Viszeralmedizin* 2014; 30:79–80.