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Review

The effects of donor age on organ transplants: A review and implications for aging research

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ABSTRACT

Despite the considerable amount of data available on the effect of donor age upon the outcomes of organ transplantation, these still represent an underutilized resource in aging research. In this review, we have compiled relevant studies that analyze the effect of donor age in graft and patient survival following liver, kidney, pancreas, heart, lung and cornea transplantation, with the aim of deriving insights into possible differential aging rates between the different organs. Overall, older donor age is associated with worse outcomes for all the organs studied. Nonetheless, the donor age from which the negative effects upon graft or patient survival starts to be significant varies between organs. In kidney transplantation, this age is within the third decade of life while the data for heart transplantation suggest a significant effect starting from donors over age 40. This threshold was less defined in liver transplantation where it ranges between 30 and 50 years. The results for the pancreas are also suggestive of a detrimental effect starting at a donor age of around 40, although these are mainly derived from simultaneous pancreas-kidney transplantation data. In lung transplantation, a clear effect was only seen for donors over 65, with negative effects of donor age upon transplantation outcomes likely beginning after age 50. Corneal transplants appear to be less affected by donor age as the majority of studies were unable to find any effect of donor age during the first few years posttransplantation. Overall, patterns of the effect of donor age in patient and graft survival were observed for several organ types and placed in the context of knowledge on aging.

1. Introduction

The progressive deterioration and loss of functionality that characterizes the aging process affects different systems and organs of the body in different ways. Through measurements at different levels, numerous microscopic, macroscopic and functional age related changes have been robustly characterized in many different tissues and organs (Craig et al., 2015). In what represents a more indirect but holistic approach, organ transplantation data give researchers the opportunity to compare the outcomes elicited by grafts from donors of different ages in order to yield novel insights into the nature and pathogenesis of organ-intrinsic aging, the effect of aged organs upon the rate and pathogenesis of organismal aging in young hosts, and the effect of a young host environment upon the rate and pathophysiology of aging in organs from elderly donors. In general, the use of transplantation data to yield insights into the nature, rate and pathophysiology of both organ and organismal aging has remained an underutilized approach within the broader field of biogerontology, despite its potential to yield novel insights into the dynamics of organ-intrinsic and organismal aging.

Since the beginning of clinical organ transplantation more than five decades ago, the outcomes of different types of transplantation have been improving, especially with regard to short-term postoperative outcomes, and the use of older donors has become more and more frequent. In 2012, the number of adult transplants in the United Kingdom alone was 2881 for kidney, 246 for pancreas, 792 for liver, 136 for heart and 179 for lung. Indeed, in the same year 35% of the donors were 60 years old or over, compared to the 14% registered in 2003 (Johnson et al., 2014). Many clinical trials and retrospective studies using different databases have analyzed the effect that the age of the donor has upon postoperative outcomes for particular organs, sometimes with conflicting results (Alexander and Vaughn, 1991; Marino et al., 1995; Keith et al., 2004; Stehlik et al., 2012; Roig et al., 2015; Bittle et al., 2013; Wakefield et al., 2015). Here, we review the literature pertaining to the main abdominal and thoracic organs used

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for transplantation, as well as for the cornea, with the aim of providing a more comprehensive analysis of the extent with which donor age affects patient outcomes for each specific organ and tissue included in our analysis, and to infer possible differences in intra-organ and inter-organ rates of aging.

2. Results

Below we review the literature on the effects of donor age on the clinical outcomes after transplantation for several organs and the cornea, with a focus on graft and patient survivals.

2.1. Liver

Marino et al. (1995) found donor age to be an independent predictor of graft failure following liver transplantation in the first 90 days post operation, as well as during the 1.12 to 2.6 years of follow-up in their retrospective double-center study with 419 adults transplanted between 1992 and 1993. The stratification of donor age into < 60 and ≥60 years old showed a significant reduction in graft survival at 23 months post operation in recipients with older donors, as well as a tendency toward the same direction when patient survival was measured. Further modeling using donor age as a continuous variable and adjusting for additional risk factors revealed no variations in the risk of graft failure for donors < 45 years old. They found that the risk of graft failure began to increase progressively with the age of the donor for donors 45 years of age and older (Marino et al., 1995). Using a larger cohort and after stratifying the donors by age into < 20, 20–29, 30–39, 40–49 and ≥50 years old, Detre et al. analyzed patient outcomes at 6-month following initial liver transplantation and found that, from donors aged 30–39, the risk of graft failure increased progressively with donor age. In the case of patient survival, the effect was not noticed until donors 40–49 years old, and did not increase further with the next age group (Detre et al., 1995). In another study with a median follow-up of three years, Feng et al. found the same progressive increase of the risk of graft failure with donor age, starting in the group of recipients with donors 40–49 years old as compared to those with donors aged < 40 years. In this case, however, additional stratification of the reference group would have been needed to know if the effect starts at an earlier donor age in this population (Feng et al., 2006).

On the other hand, in their univariate analysis, after stratifying donors according to age at 10 year intervals Hoofnagle et al. were unable to find a significant decrease in graft survival at 3, 6, 12 and 24 months for donors < 50 years of age. The multivariate analysis at 3 months, splitting donors into two groups with a cut-off age of 50, confirmed the detrimental effect of older donors on graft survival but found that this effect was largely restricted to those livers assessed by the harvesting surgeon as of poor or fair quality. When only livers that had been assessed as being of good quality were considered, the effect of donor age lost significance. Although no multivariate analysis was performed using longer follow-up times, the survival curves for graft failure showed that the first few months posttransplantation accounted for most of the difference seen in graft survival between old and young donors. Compared to graft survival, donor age showed a more moderate effect on patient survival (Hoofnagle et al., 1996). Burroughs et al. (2006) also analyzed patient survival using data of 34,664 first adult liver transplants from the European Liver Transplant Registry and found that donors 41–60 years of age had worse survival outcomes at 3 and 12 months than those aged ≤40, but better survival outcomes than those > 60.

The impact of donor age is also noticeable in the long term histology of the transplanted liver. Rifai et al. found that older donor age was associated with the presence of ductopenia and higher fibrosis scores in the biopsies from patients who were alive 10 years posttransplantation. These authors determined that donor age < 36 years old was a predictor of normal histology in the biopsies (Rifai et al., 2004). Overall, taking all these data into account together, liver donor age has a measurable impact on graft and recipient survival.

2.2. Kidney

In a study involving 50,322 patients of primary deceased donor kidney transplantation, Keith et al. found that the age of the donor was among the three main pretransplantation factors affecting long term patient survival, along with the age of the recipient and a renal diagnosis of diabetes. The stratification of donors into several age groups revealed that the 5- and 10-year patient survivals adjusted by different covariates started to decrease from donors aged 36 to 40 years. Furthermore, stratification of the recipients into < 40, 41–54, and ≥55 year age groups revealed that, for each group, older donors were associated with lower survival curves at 10 years posttransplantation (Keith et al., 2004). Oppenheimer et al. studied the cases of 3365 recipients with a functioning graft at one year after kidney transplantation and observed a linear increase in the risk of long term graft failure and patient death with increasing donor age that started to become significant for donors 30–40 years old, as compared to the reference group of < 20 years old. Their multivariate analysis also included the risk of acute rejection, which did not differ between the groups (Oppenheimer et al., 2004). Laging et al. analyzed the effect of donor age using data from living and deceased donors separately and observed that, in both cases, the risk of graft failure censored for death and uncensored graft failure started to increase exponentially from donors over 30 years old. Despite the risk curves for the two types of donors being quasiparallel, deceased donors conferred a greater risk of graft failure than living donors along all the age range studied. For deceased donor transplantation, an increased risk of graft failure was also found with pediatric donors (living donors of this age were absent) (Laging et al., 2012).

Other studies have analyzed the impact of donor age in the outcomes of kidney transplantation without providing additional information about the age at which this effect begins to be seen. Stratifying the donors into two groups with a cut-off age of 50, Moreso et al. found donor age to be an independent risk factor for graft failure for recipients who had not experienced any episodes of acute rejection. Further analysis revealed that donor age was an independent risk factor for graft failure due to chronic transplant nephropathy (Moreso et al., 1999). This condition, also known as chronic allograft nephropathy (CAN), is characterized by a progressive decline in renal function accompanied by histopathological changes affecting the glomerular, tubular, vascular and interstitial compartments, and is the main cause of late graft failure following renal transplantation (Birnbaum et al., 2009). Comparing recipients of donors 50–69 years old with those ≥70, Chavalitdhamrong et al. found transplants from older donors to increase the risk of overall graft failure, death-censored graft failure and patient death. Similar results were obtained when comparing donors 60–69 vs ≥70, but in this case the effect of donor age on death-censored graft failure was not significant (Chavalitdhamrong et al., 2008).

Along with donor age, the age of the recipient is one of the variables commonly found to affect the outcomes in organ transplantation. The interaction between donor and recipient age has been analyzed in different studies for kidney transplantation with conflicting results. In a secondary analysis of their data, Chavalitdhamrong et al. (2008) found that the kidneys from donors ≥70 years old conferred a higher risk of graft failure and patient death in recipients aged 41 to 60 than in those aged > 60. Using data from 1269 patients, 44 of whom had a donor older than 55, Waiser et al. (2000) found that kidneys from donors > 55 increased the risk of graft failure in young recipients (< 55) almost two-fold but had no significant effect in older recipients (> 55). In their univariate analysis of 201 live donor kidney transplantation recipients, Lee et al. (2014) found that the 10-year graft survival of recipients with donors > 10 years younger than the recipients was reduced in comparison to those instances in which the ages of recipient and donor were