High alcohol intake in deceased donors has no effect on pancreas graft survival: a registry analysis

R Motallebzadeh[1], M Aly[1], M El-Khairi[2], M Drage[3],

J Olsburgh[3], CJ Callaghan[3].

1- Department of Surgery, University of Cambridge, Cambridge, UK
2- Department of Statistical Science, University College London, UK
3 - Department of Nephrology and Transplantation, Guy's & St Thomas' NHS Foundation Trust, London, UK

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Author Contributions

All authors contributed extensively to the work presented in this paper.

CJC conceived the study with RM. Data collection was carried out by RM and MA. MEK carried out all statistical analyses. CJC and RM prepared the manuscript, with contributions from MD and JO. MD, JO, MA, MEK, CC and RM edited the manuscript.

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Address for correspondence:

Mr R Motallebzadeh MD PhD FRCS

Department of Surgery,

University of Cambridge,

Cambridge, UK

Email: rmz1001@yahoo.co.uk

Abbreviations

BMI - body mass index
CIT – cold ischemic time
DBD – donation after brain death
DCD – donation after circulatory death
HR – hazard ratio
NHSBT – National Health Service Blood and Transplant
SD – standard deviation
SPK – simultaneous pancreas-kidney

Abstract

Outcomes of pancreas transplantation from donors with high alcohol consumption are poorly described.

The UK Transplant Registry was used to determine if donor alcohol intake influenced pancreas survival in simultaneous pancreas-kidney (SPK) transplants performed between 2006-2012 (n=770). Recipients were stratified by donor alcohol intake: group I (n=122) – high recent alcohol intake (>21 or >14 units of alcohol/week in males or females, respectively) or previous alcohol abuse; group II (n=648) – low/unknown current intake and no previous alcohol abuse.

Median current alcohol intake was higher in group I than group II: 36.3 vs 10 units/week; $p<0.001$. One- and five-year pancreas graft survivals were 88.5% and 73.6% in group I; 87% and 74.9% in group II. There was no difference in unadjusted graft survival between groups I and II ($p=0.76$), and no difference between group II and a sub-group of group I with a donor history of alcohol abuse and high current intake ($p=0.26$), or from donors with current alcohol consumption of >50 units/week ($p=0.41$).

Pancreas donors with past alcohol abuse or current high intake are common, and graft outcomes appear to be acceptable. This analysis suggests that high donor alcohol intake, by itself, should not exclude consideration of pancreas transplantation.

Introduction

It is well recognised that excessive alcohol consumption can injure the pancreas (1). Alcohol can exert its deleterious effects on the pancreas by activating both acinar and stellate cells, resulting in autodigestive injury, progressive necro-inflammation and increased synthesis of extracellular matrix proteins leading to pancreatic fibrosis (2-4). In addition, chronic excess alcohol intake has harmful effects on the endocrine function of the pancreas with reduction in β-cell mass and insulin resistance (5, 6). There is also some evidence which suggests that high alcohol intake is associated with an increased risk of pancreatic adenocarcinoma (7-9). Therefore it is understandable that transplant surgeons are reluctant to implant pancreases from donors with a history of high alcohol consumption (10, 11). However, outcomes of pancreases transplanted from donors with high alcohol intake have been poorly described.

A large retrospective analysis of US donors found no statistically significant association between donor alcohol use and diminished pancreas graft survival, though no details were given on how alcohol consumption was quantified, or how many pancreases from donors with high alcohol use were transplanted (12). It is particularly important to examine this issue in detail as alcohol consumption appears to be rising, both in the UK, and worldwide (13, 14).

Simultaneous pancreas-kidney (SPK) transplantation has been shown to provide a strong survival benefit for selected patients with insulin-dependent

diabetes mellitus and end-stage renal failure (15). Therefore, the impact of donor alcohol intake on pancreas graft survival requires further investigation in order to prevent inappropriate decline of pancreases that may confer a survival benefit to those on the waiting list.

In this study, the UK Transplant Registry was analyzed to determine the frequency of high donor alcohol intake in SPK transplantation, and to examine whether donor alcohol intake had an impact on subsequent pancreas allograft survival. We also performed subgroup analyses to determine whether past alcohol abuse or current high intake had differing effects on graft outcome.

Materials & Methods

Data on SPK transplants performed between 1 January 2006 and 31 December 2012 were identified from the National Health Service Blood and Transplant (NHSBT) UK Transplant Registry. During this time period there were 9 pancreas transplant units in the UK, but one unit performed only three SPK transplants and closed in 2006. The UK pancreas allocation schemes between 2006 and 2012 are described elsewhere (16).

Organs were procured from donation after brain death (DBD) or Maastricht category III and IV donation after circulatory death (DCD) donors. Study exclusion criteria were chosen to minimize possible differences in baseline donor, recipient, and operative characteristics between donors with or without a history of high alcohol intake. Exclusion criteria were: Maastricht category I or II DCD donors, pediatric donors (aged less than 18 years), donor age >55 years, donor body mass index (BMI) <20 or >30 kg/m^2, and recipients of previous solid organ transplants.

Donor alcohol intake was recorded electronically by donor co-ordinators after interviews with donor families where questions were specifically asked on donor alcohol intake, including current alcohol intake and past history of alcohol abuse. Alcohol abuse was not specifically defined; duration of alcohol abuse was not generally recorded. Donor co-ordinators also examined the donor's medical records, and, where possible, contacted the donor's family physician prior to donation.

Where the current volume and type of alcohol ingested by the donor was documented by the donor co-ordinator, the units of alcohol consumed per week in the period prior to donation were calculated (17). In the UK, one unit of alcohol is defined as 10 ml of pure alcohol (18); for example, two standard (175 ml) glasses of white wine (13% alcohol by volume) per day is equivalent to 32.2 units/week. The UK government recommended maximum alcohol intake of 21 units/week for men and 14 units/week for women was used to define high / low current alcohol intake (19, 20).

Recipients were initially stratified into two groups based on the recorded donor alcohol history: group I – high current intake or past history of alcohol abuse; group II – low (or unknown) current alcohol intake and no known history of alcohol abuse. For some analyses, group I was further subdivided: Ia – high current intake and no (or unknown) past history of alcohol abuse; Ib – past history of alcohol abuse but current alcohol intake unknown; Ic – past history of alcohol abuse and high current alcohol intake; Id - past history of alcohol abuse and low current intake. In addition, within group I, donors with current alcohol intake >50 units per week were also identified.

Pancreas graft failure was defined as return to insulin dependence, with censoring for death with a functioning graft and grafts still functioning at the time of last follow-up.

Statistical analysis

Differences in donor and recipient characteristics between the two groups were determined using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Survival functions were estimated according to the Kaplan–Meier method, with groups compared using the log-rank test. $P < 0.05$ was considered significant.

Univariate Cox proportional hazards models were used to identify variables associated with pancreas graft survival. Hazard ratios (HRs) and 95% confidence intervals were calculated for each variable. A multivariate Cox proportional hazards model was used to determine if donor alcohol consumption was associated with pancreas graft survival after adjusting for other variables known to affect pancreas graft survival (donor gender, age, BMI, cause of death, graft cold ischemic time [CIT] and recipient age). Statistical analyses were performed using PRISM version 6 (GraphPad Software, La Jolla, CA, USA) and R: A Language and Environment for Statistical Computing version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 770 SPK transplants met our inclusion criteria. Based on the history of donor alcohol consumption, there were 122 (15.8%) recipients in group I and 648 (84.2%) in group II.

Donor, recipient and operative characteristics

Donor, recipient, and operative characteristics are shown in Table 1. Donors in group I were older, more likely to be male, and were less likely to have had an atraumatic cause of death when compared to donors in group II. As expected, donors in group I had a current weekly alcohol intake that was much higher than those in group II. There were no statistically significant differences in recipient variables between the two groups. Pancreas cold ischemic time (CIT) was significantly longer in group II than group I, although CITs were generally short in both groups.

Detailed analysis of donor alcohol intake was undertaken. Data on current alcohol intake were available for 130 donors (16.9%); 88 in group I (72.1%) and 42 in group II (6.5%). These data are shown in Figure 1 and stratified according to donor gender. Twenty-six donors had current alcohol intake >50 units per week; this equates to more than 7 single shots of spirits (25 mL of 40% alcohol by volume) per day. For group I donors, the median (IQR) alcohol intake was higher in males than females (26 (13.3-49.7) versus 21 (8.6-41.5) units per week), but this did not reach statistical significance (p=0.11). Unsurprisingly, the majority of donors within group I had a past history of alcohol abuse (69/122 – 57%). Overall, history of alcohol abuse was

documented as “unknown” for 20 donors (2.6%); three in group I (2.5%) and 17 in group II (2.6%).

In order to determine if a past history of alcohol abuse, or high current intake (or both), were associated with pancreas graft survival, further stratification of group I was undertaken (Table 2). The majority of donors in group I had high current intake and no (or unknown) past history of alcohol abuse (group Ia). Of note, group Ic (n=37) contained donors with a past history of alcohol abuse and high current intake, with a median (IQR) alcohol consumption of 50 (31.5-70.7) units per week.

Over the study period the usage of pancreases from donors with a high current alcohol intake or past history of alcohol abuse did not change (Supplementary Figure 1). There were variations between centers in the use of donors with high alcohol intake (Supplementary Figure 2).

Graft and patient survival

There were 8 deaths (6.6%) in group I and 60 (9.3%) in group II recipients within the study period (Figure 2a); there was no statistically significant difference in overall patient survival between the two groups (p=0.39).

Unadjusted death-censored pancreas graft survival was similar for both groups (Figure 2b). One- and five-year pancreatic graft survivals were 88.5% and 73.6% in group I and 87% and 74.9% in group II, respectively. Overall, there was no evidence of a difference in unadjusted graft survival between the

two groups (p=0.76). Graft survival did not significantly differ between the sub-groups of group I, and group II (p=0.11; Figure 2c), nor between groups Ic and II when these were compared directly (p=0.26). There was no difference in death-censored pancreas graft survival in SPK transplants from donors with current alcohol consumption of >50 units per week (n=26), versus donors in group II (p=0.41; graph not shown).

In a univariate Cox proportional hazards regression analysis (Table 3), significant factors associated with pancreas graft survival were donor age (p=0.02) and pancreas CIT (p=0.02). In a multivariate Cox regression analysis (Table 3), only pancreas CIT was associated with graft survival (HR=1.05 per hour, p=0.02). Donor alcohol intake (current, or past history of abuse) was not a risk factor for worse pancreas graft survival.

Discussion

This study investigated the effect of donor alcohol consumption on pancreas graft survival. Donor alcohol consumption above recommended UK thresholds is not uncommon in SPK transplants, and a small proportion of donors (4.8%) have a history of both alcohol abuse and high current intake. In both univariate and multivariate analyses, donor alcohol intake appeared to have no deleterious impact on medium-term pancreas graft survival. Furthermore, analyses of subgroups of donors that had the strongest pre-morbid alcohol history did not reveal significantly worse pancreas graft survival.

The findings of this study are highly relevant to the utilisation of donor pancreases. Previous work has shown that a high proportion of pancreases that are offered for allocation are not transplanted, often due to perceived unfavorable donor characteristics (e.g. age, BMI, elevated serum amylase) or the appearance or consistency of the pancreas at the time of recovery of organs or bench-work (21-25). Furthermore, the pancreas is more vulnerable to intra-operative injury than other abdominal organs during recovery of organs (26). As a result, the conversion rate from potential pancreas donor to implantation in a recipient is low; registry data show that only 70% of potential donor pancreases offered for donation are recovered, and of these, a further 30-50% are discarded after recovery of organs has been completed (26, 27). If pancreases are not utilized due to a perceived risk of high donor alcohol intake this will prolong waiting times for patients listed for a SPK transplant. The results of this study suggest that high donor alcohol intake is not a reason, in itself, to decline a pancreas offer or a procured pancreas.

This is perhaps surprising, as excess alcohol consumption has been shown to be consistently associated with development of pancreatitis, with the risk rising in a dose-dependent manner (28). A minimum of 6–12 years of approximately 80 mL or more of alcohol per day is considered necessary for the development of clinically evident pancreatitis. The pathophysiologic pathways underlying alcohol-induced pancreatitis have not yet been fully elucidated, though it is known that direct acinar cell damage is mediated by alcohol and its metabolites (e.g. acetaldehyde and fatty acid ethyl esters), and that inflammatory cell recruitment and activation are critical components of alcoholic pancreatitis (2, 29, 30). The production of pro-inflammatory cytokines, e.g. TNFα, can in turn activate pancreatic stellate cells to develop a myofibroblastic phenotype, leading to fibrin deposition and scarring (31, 32). Chronic alcohol consumption is therefore the major risk factor for chronic pancreatitis, with development of pancreatic fibrosis and progressive loss of normal parenchymal architecture, potentially leading to exocrine and endocrine pancreatic insufficiency, and increasing the risk of pancreatic cancer (33, 34).

A possible explanation for the apparent lack of association between donor alcohol consumption and pancreas graft survival is that only donor pancreases with minimal or absent macroscopic features of pancreatic pathology are likely to be transplanted. Macroscopic findings consistent with chronic pancreatitis have been reported in only 18% of autopsies performed on patients with a history of alcohol abuse and liver disease, implying that many could have had normal functioning pancreases (35). As the effect of

alcohol on pancreatic inflammation is influenced by other environmental or genetic factors (e.g. ethnicity and polymorphisms in ethanol-metabolizing enzymes), less than 10% of heavy drinkers develop clinically significant pancreatitis (28, 36-39). All pancreases should be assessed carefully at bench-work; those from donors with high alcohol intake should be inspected especially carefully for the presence of fibrosis, fatty infiltration, pancreatitis, and parenchymal masses.

Although our study is the first large investigation that specifically addresses the impact of donor alcohol intake on pancreas graft survival, the authors acknowledge its limitations. Firstly, quantifying donor alcohol intake through questioning of the donor family at a highly stressful time is likely to be somewhat imprecise. It is difficult to estimate the magnitude of any potential bias, as validation of donor alcohol intake is not feasible. In many cases, the donor alcohol history was unknown, and it is possible that a significant number of donors in group II had a heavy alcohol intake, reducing the likelihood of finding an association between alcohol consumption and poor graft outcome. Duration of donor alcohol abuse was not generally recorded and the term ‘alcohol abuse’ was not defined. Secondly, we chose a threshold for excess alcohol intake in donors as that set by UK government guidelines on ‘safe’ drinking (20, 40). Regular alcohol consumption above this level represents an increase in the lifetime risk of death by 1%, but this long-term risk may not be relevant in the context of SPK transplantation. However, sub-group analysis of those donors known to have very high alcohol intake did not identify this as a poor prognostic factor. It is possible that this group was

under-powered to detect an association. Thirdly, it is possible that high donor alcohol intake may be relevant in more 'marginal' donors (e.g. aged >55 years, BMI >30 kg/m^2); however, the number of pancreases implanted from such donors during the study period was small, and as surgeons would be expected to be less likely to implant pancreases from older, heavier donors with high alcohol intake, this would make outcome analyses more unreliable. Fourthly, due to lack of electronically recorded information on donor alcohol use prior to 2006, analysis of SPK transplants before this date was precluded and therefore the pancreas graft survival in this study reflects medium-term outcome only. Finally, the incidence of post-transplant pancreatitis, peri-pancreatic collections, and donor duodenal segment leaks would also be of interest, but this data was not captured by the UK Transplant Registry. The causes of graft loss may also differ between the groups of patients, but immunological and non-immunological causes of pancreas graft loss can be difficult to distinguish, and are often not coded accurately in registry analyses

Despite these limitations, we feel that this study provides some reassurance for surgeons considering pancreases from donors with an increased alcohol intake, though these organs require cautious back-table assessment. Excessive donor alcohol intake, by itself, should not exclude consideration of pancreas utilisation.

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