Nephrol Dial Transplant (2015) 0: 1–9
doi: 10.1093/ndt/gfv214

ndt Nephrology Dialysis Transplantation

Original Article

Recipient obesity and outcomes after kidney transplantation: a systematic review and meta-analysis

Christopher J. Hill[1], Aisling E. Courtney[1], Christopher R. Cardwell[2], Alexander P. Maxwell[1], Giuseppe Lucarelli[3], Massimiliano Veroux[4], Frederico Furriel[5], Robert M. Cannon[6], Ellen K. Hoogeveen[7], Mona Doshi[8] and Jennifer A. McCaughan[1]

[1]Regional Nephrology Unit, Belfast City Hospital, Belfast, UK, [2]Centre for Public Health, Queen's University Belfast, Belfast, UK, [3]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy, [4]Vascular Surgery and Organ Transplant Unit, University of Catania, Catania, Italy, [5]Department of Urology and Renal Transplantation, University Hospital, Coimbra, Portugal, [6]Department of Surgery, University of Louisville, Louisville, KY, USA, [7]Department of Nephrology, Leiden University Medical Centre, Leiden, The Netherlands and [8]Department of Internal Medicine, Wayne State University, Detroit, MI, USA

Correspondence and offprint requests to: Jennifer A. McCaughan; E-mail: jamccaughan@doctors.org.uk

ABSTRACT

Background. The prevalence of obesity is increasing globally and is associated with chronic kidney disease and premature mortality. However, the impact of recipient obesity on kidney transplant outcomes remains unclear. This study aimed to investigate the association between recipient obesity and mortality, death-censored graft loss and delayed graft function (DGF) following kidney transplantation.

Methods. A systematic review and meta-analysis was conducted using Medline, Embase and the Cochrane Library. Observational studies or randomized controlled trials investigating the association between recipient obesity at transplantation and mortality, death-censored graft loss and DGF were included. Obesity was defined as a body mass index (BMI) of ≥30 kg/m^2. Obese recipients were compared with those with a normal BMI (18.5–24.9 kg/m^2). Pooled estimates of hazard ratios (HRs) for patient mortality or death-censored graft loss and odds ratios (ORs) for DGF were calculated.

Results. Seventeen studies including 138 081 patients were analysed. After adjustment, there was no significant difference in mortality risk in obese recipients [HR = 1.24, 95% confidence interval (CI) = 0.90–1.70, studies = 5, n = 83 416]. However, obesity was associated with an increased risk of death-censored graft loss (HR = 1.06, 95% CI = 1.01–1.12, studies = 5, n = 83 416) and an increased likelihood of DGF (OR = 1.68, 95% CI = 1.39–2.03, studies = 4, n = 28 847).

Conclusions. Despite having a much higher likelihood of DGF, obese transplant recipients have only a slightly increased risk of graft loss and experience similar survival to recipients with normal BMI.

Keywords: graft survival, kidney transplantation, mortality, obesity

INTRODUCTION

The global epidemic of obesity is reflected in the renal transplant population where the proportion of recipients with a body mass index (BMI) in excess of 30 kg/m^2 is doubling every 15 years [1–3]. However, the impact of recipient obesity on long-term graft and recipient outcomes is unclear.

Obesity may be detrimental to recipient survival via its association with early post-operative complications as well as with other chronic medical conditions such as type 2 diabetes mellitus, cardiovascular disease and chronic respiratory disorders [4–7]. All of these conditions are associated with increased mortality risk in the general population and may be expected to be similarly influential in renal transplant recipients. However, it has recently been reported that renal transplantation

confers a similar survival benefit in obese recipients as in those with a normal BMI when compared with maintenance dialysis in the first year after transplantation [8].

In theory, obesity could influence renal allograft outcome in the short and long terms by a number of mechanisms. In the general population, obesity is associated with the development of proteinuria and a reduced glomerular filtration rate (GFR) [5, 9–11]. Although a causal mechanism has yet to be fully established, obesity-related chronic kidney disease (CKD) may develop through a combination of immunological and non-immunological mechanisms—these include hyperfiltration, associated conditions such as diabetic nephropathy and renal injury promoted by pro-inflammatory cytokines produced by adipose tissue [12–14]. In some patients with obesity-related CKD, it has been demonstrated that weight loss can result in regression of proteinuria, although there is a lack of evidence with respect to its long-term effect on stabilization of GFR [15]. Damage to transplanted kidneys may be caused by similar pathophysiological mechanisms to those which occur in the native kidneys of obese patients. In addition, there is also some evidence that obesity may alter the metabolism and bioavailability of immunosuppressive medications, thus potentially exposing the renal allograft to chronic immunological injury [16].

Obese individuals undergoing abdominal surgery also have more frequent anaesthetic complications, increased incidence of wound infections and longer hospital admissions compared with the non-obese population [17, 18]. In renal transplantation, recipient obesity is associated with prolonged surgical times and an increased risk of peri-operative complications [1, 19–21]. This may have an impact upon early graft outcome measures, such as the incidence of delayed graft function (DGF) [22], and could result in premature graft loss [23].

Obesity is a common, and potentially modifiable, condition in the CKD and renal transplant population. In this study, we aimed to establish the association between obesity and death-censored graft survival as well as recipient survival. The risk of DGF was investigated as a sensitivity analysis.

MATERIALS AND METHODS

Search strategy

A systematic search was undertaken in accordance with recognized methods. Medline, Embase and the Cochrane Library were searched for studies published between each database's inception date and 31 May 2013. Search terms are detailed in the Supplementary data, Table S1. Reference lists of included studies were also searched.

Inclusion/exclusion criteria

Reports were screened independently by two authors (CJH/JAM). Where there was any disagreement, a third author (AEC) was consulted. Obesity was defined using the World Health Organization definition of a BMI of ≥30 kg/m^2 [24]. Studies were included that assessed the association between obesity at the time of transplantation and one or more of the following transplant-related outcomes: DGF, death-censored graft survival and recipient survival. Only studies that assessed outcomes in adult patients were included. We accepted study authors' definitions of DGF. Studies were excluded if they used alternative anthropometric measures to define obesity or if the BMI was analysed as a continuous variable. Studies focussing on multi-organ transplants were also excluded as were those studies that were published only in abstract format. In order to minimize the risk of duplication of data, where sampling periods of two studies overlapped such that a patient could have been included in both, one of the studies was excluded. Where authors responded to data requests, these studies were included or, if no reply was received, the larger of the two overlapping studies was used.

Statistical analysis

Due to differing reporting methods, study authors were contacted and asked to provide clarification of results or re-analyse data. Where study authors did not reply, unadjusted data were extracted from published manuscripts using previously described methodology (Table 1) [25]. Cox proportional hazards regression was used to generate hazard ratios (HRs) to investigate the risk of death-censored graft loss and overall risk of death. Patients with a normal BMI (18.5–24.9 kg/m^2) were used as the reference category for generation of HRs. An *a priori* sensitivity analysis was undertaken to investigate the association between obesity and the likelihood of DGF. Odds ratios (ORs) of the likelihood of DGF were calculated (using patients with a normal BMI as the reference category). Logarithms of ORs and HRs (and their corresponding standard errors) were used to generate pooled estimates using Revman version 5.2.6 (Nordic Cochrane Centre, The Cochrane Collaboration). Study heterogeneity was assessed using the χ^2 test and I^2 statistic [26]. Study heterogeneity was anticipated due to the use of observational data only; therefore, random effects models were used to generate pooled estimates [27]. Publication bias was assessed using funnel plots, Egger's test, Begg's test and trim and fill methodology.

All study methodology conformed to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria [42].

RESULTS

Database searches identified 6963 records (Supplementary data, Figure S1). After application of inclusion and exclusion criteria, 17 studies remained for inclusion in the quantitative synthesis [19, 20, 22, 28–41]. The total number of patients analysed from the included studies was 138 081. Characteristics of included studies are detailed in Table 1. Studies that did not meet inclusion criteria are detailed in the Supplementary data, Table S2. The Newcastle–Ottawa scale was used to assess study quality (Supplementary data, Table S3) [43]. In brief, all included studies were observational in nature, nine of which were single-centre studies. In the published manuscripts, recipient survival was assessed in 8 studies [19, 20, 28, 31, 35, 36, 38, 39] and death-censored graft survival was assessed in 10 studies [19, 20, 28, 31, 33, 35–39]. The likelihood of DGF was assessed in 12 studies. DGF was defined as the need for dialysis within

Table 1. Characteristics of included studies

Study	Study type	Participants	Original study analysis	Adjustments available for meta-analysis	Follow-up	Data available		
						DGF	Graft survival	Recipient survival
Aalten *et al.* [28], the Netherlands	Retrospective observational study	2067 transplant recipients in the Netherlands Organ Transplant Registry from 1994 to 2006	1. BMI ≥ 30 kg/m^2 compared with <30 kg/m^2 2. BMI categorized as <19, 19–22, 22–25, 25–28, 28–31, 31–34, ≥34 kg/m^2	Unadjusted only	Median (IQR), 2 (0.25–5) years		✓	✓
Abou-Jaoude *et al.* [29], Lebanon	Retrospective observational study	137 transplant recipients from 1998 to 2007	1. BMI categorized as <18.5, 18.5–24.9, 25–29.9, >30 kg/m^2	Unadjusted only	Not stated	✓		
Bardonnaud *et al.* [30], France	Retrospective single-centre observational study	200 transplant recipients from 2004 to 2008	1. BMI ≥ 30 kg/m^2 compared with <30 kg/m^2	Unadjusted only	Not stated	✓		
Cannon *et al.* [19], USA	Retrospective observational study	74 983 recipients in the United Network for Organ Sharing database from 2004 to 2009	1. BMI categorized as <30, 30–<35, 35–<40, ≥40 kg/m^2	Recipient age, gender, diabetes, hypertension, ethnicity, donor type—live versus deceased, peak PRA, HLA mismatch, donor CVA, prior transplant	Not stated	✓	✓	✓
Chang *et al.* [20], Australia and New Zealand	Retrospective observational study	5684 recipients in the Australia and New Zealand Dialysis and Transplant Registry from 1991 to 2004	1. BMI categorized as <18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2	Recipient age, gender, ethnicity, diabetes, smoking status, cardiovascular co-morbidities at RRT start, year of transplant, dialysis duration, donor age, donor type, HLA mismatch, most recent PRA, total ischaemic time and calcineurin inhibitor (ciclosporin versus tacrolimus)	Not stated	✓	✓	✓
Ditonno *et al.* [31], Italy	Retrospective single-centre observational study	563 deceased donor recipients from 2000 to 2008	1. BMI categorized as <18.5, 18.6–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2	Recipient age, gender, ethnicity, diabetes, hypertension, donor age, HLA mismatch, peak PRA, donor CVA and cold ischaemic time	Mean 53 months	✓	✓	✓
Doshi *et al.* [32], USA	Retrospective observational study	10 764 deceased donor recipients in the United Network for Organ Sharing database from 1994 to 2004	1. BMI > 30 kg/m^2 compared with ≤30 kg/m^2	Recipient age, gender, ethnicity, cause of ESRD, hepatitis C status, peak PRA, pre-emptive transplant, waiting time, HLA mismatch, donor: recipient size mismatch, cold ischaemic time, pulsatile perfusion	Not stated	✓		
Furriel *et al.* [33], Portugal	Retrospective single-centre observational study	448 transplant recipients from 1984 to 2008	1. BMI categorized as 18.5–24.9, 25–29.9, ≥30 kg/m^2	Unadjusted only	Mean 6.7 years in normal BMI group, 7.9 years in obese group	✓	✓	
Gore *et al.* [34], USA	Retrospective observational study	27 377 transplant recipients in the United Network for Organ Sharing Database from 1997 to 1999	1. BMI categorized as <18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥35 kg/m^2	Unadjusted only	Not stated	✓		

Continued

Table 1. Continued

Study	Study type	Participants	Original study analysis	Adjustments available for meta-analysis	Follow-up	Data available		
						DGF	Graft survival	Recipient survival
Grosso *et al.* [35], Italy	Retrospective single-centre observational study	376 transplant recipients	1. BMI categorized as <25, 25–30, >30 kg/m^2	Unadjusted only	Mean (SD), 13.6 (5.2) years	✓	✓	✓
Halme *et al.* [36], Finland	Retrospective single-centre observational study	276 transplant recipients from 1972 to 1993	1. BMI ≥ 30 kg/m^2 compared with those with BMI 20–25 kg/m^2	Unadjusted only	Not stated		✓	✓
Holley *et al.* [37], USA	Retrospective single-centre observational study	96 deceased donor recipients from 1986 to 1988	1. BMI ≥ 30 kg/m^2 compared with BMI ≤ 27 kg/m^2 in males, ≤25 kg/m^2 in females	Unadjusted only	2-year follow-up period		✓	
Hoogeveen *et al.* [38], the Netherlands	Retrospective observational study	1810 transplant recipients in the Netherlands Organ Transplantation Registry from 1984 to 1997	1. BMI categorized as ≤20, 20–25, 25–30, >30 kg/m^2	Recipient survival adjusted for recipient gender, recipient age, smoking status, cardiovascular disease, diabetes and hypertension Graft survival adjusted for the above and donor age, donor type (live versus deceased donor) and cold ischaemic time	Not stated		✓	✓
Modlin *et al.* [39], USA	Retrospective single-centre observational study	254 transplant recipients from 1970 to 1990	1. BMI > 30 kg/m^2 compared with <27 kg/m^2	Unadjusted only	Mean (SD), 58.9 (40) months		✓	✓
Molnar *et al.* [22], USA	Retrospective observational study	11 836 transplant recipients in the Scientific Registry of Transplant Recipients from 2001 to 2007	1. BMI categorized as ≤19.99, 20–21.99, 22–24.99, 25–29.99, 30–34.99, ≥35 kg/m^2	Adjusted for age, gender, ethnicity, diabetes, dialysis vintage, insurance type, marital status, standardized mortality ratio of dialysis clinic, spKt/V, dialysis access, protein catabolic rate, albumin, creatinine, total iron-binding capacity, ferritin, phosphorous, calcium, bicarbonate, white cell count, lymphocyte percentage, haemoglobin, donor type (live or deceased donor), donor age, panel reactive antibody, HLA mismatch, cold ischaemic time, transfusion history and extended donor criteria[a]	Not stated	✓		
Singh *et al.* [40], Canada	Retrospective single-centre observational study	78 transplant recipients from 1999 to 2002	1. BMI > 30 kg/m^2 compared with those with BMI <30 kg/m^2	Unadjusted only	Not stated	✓		
Weissenbacher *et al.* [41], Austria	Retrospective single-centre observational study	1132 deceased donor recipients from 2000 to 2009	1. BMI categorized as <18.5, 18.5–24.9, 25–29.9, >30 kg/m^2	Unadjusted only	Not stated	✓		

[a]Data from Molnar and colleagues included in analyses compared BMI > 30 with BMI ≤ 30 kg/m^2. IQR, interquartile range; PRA, panel reactive antibodies; HLA, human leucocyte antigen; CVA, cerebrovascular accident.

1 week of transplantation in six studies [19, 22, 30, 32, 34, 41], as the need for dialysis within 72 h of transplantation in one study [20] and was not defined in five studies [29, 31, 33, 35, 40].

Where insufficient data were available in the published study, the corresponding author was contacted and asked to provide either anonymized individual patient data or re-analyse results

according to pre-specified criteria. Anonymized individual patient data or re-analysed results were provided by five study authors [19, 31, 33, 35, 38]. Covariates available for adjustment are shown in Table 1. Ten study authors did not respond, and these could only be included in unadjusted analyses [28–30, 33, 34, 36, 37, 39–41]. The studies included in unadjusted analyses did not all compare patients with a BMI of ≥30 kg/m^2 to those with a BMI of 18.5–24.9 kg/m^2. BMI categories used in contributing studies are documented in Table 1.

Mortality

Eight studies [19, 20, 28, 31, 35, 36, 38, 39] contributed to the unadjusted analysis of patient survival (Supplementary data, Figure S2). In the unadjusted analysis, the HR [95% confidence interval (CI)] for risk of death in obese transplant recipients was 1.76 (1.39–2.21) when compared with patients with a normal BMI. In the five studies where covariates were available for adjustment, the unadjusted HR (95% CI) was 1.51 (1.20–1.89) [19, 20, 31, 35, 38]. After adjustment, there was no significant difference in the risk of death between obese patients and those with a normal BMI; HR (95% CI), 1.24 (0.90–1.70) (Figure 1A). However, there was significant heterogeneity present (I^2 81%, P for heterogeneity <0.001).

Death-censored graft loss

Ten studies [19, 20, 28, 31, 33, 35–39] contributed to the unadjusted analysis of risk of graft loss (Supplementary data, Figure S3). The unadjusted HR (95% CI) of death-censored graft loss was 1.52 (1.24–1.85). However, there was significant associated heterogeneity (I^2 76%, P for heterogeneity <0.001). Only five studies contributed to the adjusted analysis [19, 20, 31, 35, 38]. In these five studies, the unadjusted HR (95% CI) was 1.21 (1.15–1.28). After adjustment, there was a small but statistically significant increased risk of death-censored graft loss; HR (95% CI), 1.06 (1.01–1.12) (Figure 1B). There was no associated heterogeneity (I^2 0%, P for heterogeneity 0.6).

Sensitivity analysis of likelihood of delayed graft function

Eleven studies [19, 22, 29–35, 40, 41] contributed to the unadjusted analysis of likelihood of DGF (Supplementary data, Figure S4). The unadjusted OR (95% CI) for DGF was significantly increased 1.76 (1.52–2.04); however, this was associated

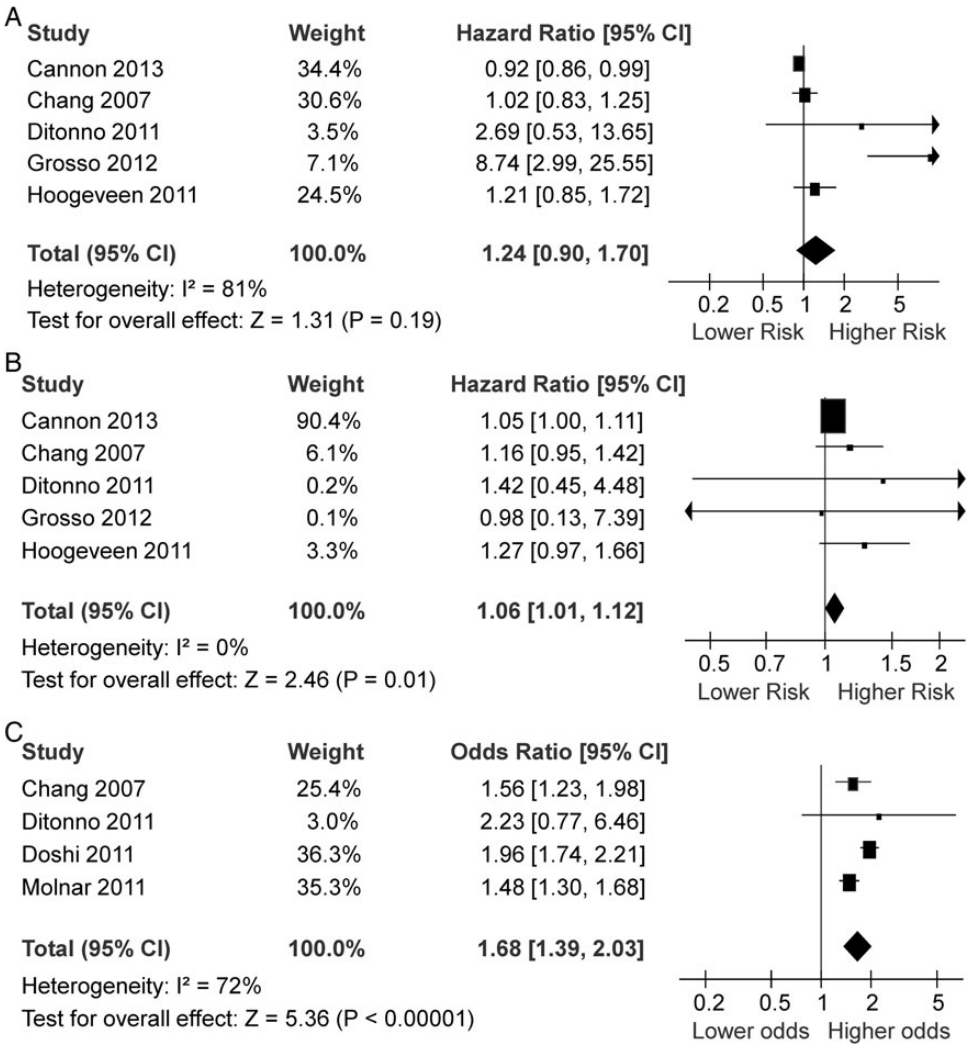

FIGURE 1: Adjusted pooled estimates of HRs of mortality risk (**A**), HRs of risk of death-censored graft loss (**B**) and ORs of delayed graft function (**C**).

with significant heterogeneity (I^2 62%, P for heterogeneity 0.05). Only four studies contributed to the adjusted analysis [20, 22, 31, 32]. The unadjusted OR (95% CI) for DGF in these studies was 1.76 (1.42–2.18). After adjustment, the OR (95% CI) for DGF remained elevated at 1.68 (1.39–2.03) with significant heterogeneity (I^2 72%, P for heterogeneity 0.01) present (Figure 1C).

Assessment of publication bias

Funnel plots were only generated for unadjusted analyses as the lower numbers of studies included in adjusted analyses meant interpretation of the plots was challenging (Supplementary data, Figures S5–S7). There was evidence of asymmetry (Egger's test P 0.02, Begg's test P 0.9) in the plot for the recipient survival analysis where larger studies observing smaller effects of obesity on mortality risk could reflect publication bias. Similarly, there appeared to be funnel plot asymmetry in the studies of obesity and DGF, which again indicated that larger studies tended to observe smaller effects (Egger's test P 0.03, Begg's test P 0.2). Trim and fill analysis was also performed, which resulted in minimal alteration to the reported results. The funnel plot for the death-censored graft survival analysis showed little evidence of asymmetry suggesting that publication bias was unlikely to have been present (Egger's test P 0.1, Begg's test P 0.6).

DISCUSSION

The increased prevalence of obesity has implications for both kidney transplant recipients and transplant programmes. In this systematic review and meta-analysis, we were unable to detect a significant difference in mortality risk between obese transplant recipients and those with a normal BMI after adjustment for common co-morbidities and transplant-related factors. In contrast, obese kidney transplant recipients had a higher likelihood of DGF and death-censored graft loss when compared with those who had a normal BMI at the time of transplantation.

Obesity is a major public health issue in many countries [44, 45]. It is also increasingly common amongst CKD patients, some of whom will be considered for renal transplantation [2, 11, 46]. In the general population, obesity is associated with increased mortality risk primarily due to cardiovascular disease. In this meta-analysis, recipient obesity was not associated with an increased risk of death compared with recipients with a normal BMI. While this initially appears counter-intuitive, due to the increased prevalence of common co-morbidities such as hypertension and diabetes mellitus in obese individuals, there are a number of possible explanations. Firstly, renal transplant recipients have already acquired a substantially increased risk of cardiovascular morbidity by virtue of their development of end-stage renal disease (ESRD) [47]. It is possible that the additional cardiovascular risk, conferred by obesity, is undetectable in the presence of ESRD. Secondly, the relationship between BMI and survival in the haemodialysis population may be relevant. Paradoxically, in patients on maintenance haemodialysis and those on the transplant waiting list, a low BMI is associated with an increased mortality risk [48, 49]. This may reflect a combination of underlying comorbidity, protein-energy malnutrition and the existence of a chronic inflammatory state as opposed to a directly protective effect of adiposity [50]. Potential transplant recipients who do not have a low BMI may be more likely to be clinically well, with optimized nutrition and minimal chronic inflammation, thus rendering them fitter to undergo the physiological stresses associated with transplantation. Thirdly, the absence of an association between recipient obesity and elevated mortality risk could relate to inherent selection bias in studies investigating survival in renal transplantation. Individuals with CKD undergo rigorous assessment prior to activation on the transplant waiting list, and those with significant co-morbidities, such as severe cardiovascular disease, may not be listed [51]. Gill and colleagues recently reported that recipients with a BMI of $\geq$30 kg/m^2 had an equivalent reduction in mortality to non-obese recipients following transplantation when compared with BMI-matched individuals remaining on the transplant waiting list [8]. Regardless of the explanation, survival following kidney transplantation in this study was comparable between obese persons and those with a normal BMI.

This meta-analysis also demonstrated a small, but statistically significant, increased risk of death-censored graft loss. Obesity may result in the development of hyperfiltration and proteinuria leading to glomerulosclerosis with a consequent reduction in GFR [9, 52]. Traditionally, the renal injury that occurred in obese patients was assumed to be primarily haemodynamic in nature. However, it is now recognized that adipose tissue has both endocrine and immunological functions that could contribute to renal damage. Obese patients have elevated levels of pro-inflammatory cytokines, such as tumour necrosis factor alpha, that may mediate glomerular injury [14, 53]. Other products of adipose tissue, including certain adipokines, increase insulin resistance and could result in glomerular damage through altered endothelial cell function [53]. It is possible that these mediators contributed to the increased risk of death-censored graft loss documented in this study. It is also possible that the changes in drug metabolism associated with obesity may impact long-term graft survival. Previous studies have demonstrated the difficulties in maintaining adequate serum concentrations of calcineurin inhibitors in obese patients; sub-therapeutic immunosuppression could predispose to immunologically mediated graft injury [16]. A recent publication described an association between a recipient BMI exceeding 35 kg/m^2 and biopsy-proven acute rejection [54]. In this cohort, adjustment for biopsy-proven acute rejection significantly attenuated the HR for death-censored graft loss among very obese recipients. This may reflect the challenge of achieving early therapeutic levels of immunosuppression in these patients whose body composition differs significantly from transplant recipients with a normal BMI.

In this meta-analysis, obesity was associated with a 68% increase in the odds of DGF. DGF has been attributed to both ischaemic and immunological injuries. Molnar and colleagues hypothesized that obesity could cause DGF through a combination of vasoconstriction (due to elevated sympathetic nervous system activity) and protracted operative time [22]. The higher incidence of post-operative medical and surgical complications

that have been documented in obese transplant recipients could also increase the likelihood of DGF [21, 55]. Transplantation is inevitably associated with a variable amount of ischaemic insult to the allograft, which could be further compounded in obese recipients by haemodynamic instability or toxic insults.

The major strength of this meta-analysis is the large number of transplant recipients included. A previous meta-analysis has aimed to address the impact of recipient obesity on outcomes following renal transplantation, but this is the largest study to investigate these associations [54]. The studies included in this meta-analysis were also drawn from a variety of countries, which increases its applicability across a number of healthcare systems and organ transplantation programmes. A further strength was the use of results from pre-specified re-analyses that allowed consistent categorization of recipients according to BMI across studies. It was not possible to develop a standard set of covariates to use in adjusted analyses due to heterogeneity in reporting methods of contributing studies. However, in the majority of studies contributing to adjusted analyses, the list of covariates incorporated recipient characteristics (such as age, gender and co-morbid conditions), donor factors (such as the type of transplant—live donor versus deceased donor) and other transplant-related features (such as HLA mismatch and cold ischaemic time).

This study has potential limitations. Firstly, only a limited number of studies had adjusted results available, increasing the risk of Type 2 error. This meant some of the adjusted analyses were substantially influenced by the results of large individual studies. However, as an *a posteriori* analysis, studies were sequentially removed from each adjusted analysis to assess the effect of individual study weighting. The results of the analyses of recipient survival, graft survival and DGF all remained similar despite removal of some of the larger studies. As discussed, there was also some variability in the nature of covariates across studies. Conceivably donor, recipient and surgical factors could impact upon both recipient and graft outcomes; therefore, it would have been preferable to adjust for a standard set of covariates. The HR of death-censored graft loss shifted substantially following adjustment for a limited set of covariates such that the adjusted HR in obese recipients only just reached statistical significance. It is possible that the effect seen in this meta-analysis could have disappeared with adjustment for other factors. In particular, we were unable to adjust for pharmacological covariates such as immunosuppressive regimens that could influence graft outcomes [56]. Differences between studies with respect to covariates could also have contributed to the high heterogeneity seen in some results such as the adjusted HR for recipient mortality. Secondly, some studies have suggested that transplant outcomes worsen when recipient BMI exceeds 40 kg/m^2 [8]. Ideally, further sub-categorization of BMI, e.g. 30–34.9, 35–39.9 and ≥40 kg/m^2, would have been useful. Unfortunately, individual patient data were not available from all included studies that precluded any further sub-categorization. Therefore, based on the results in this meta-analysis, it is not possible to comment on the effect of very high BMI (>40 kg/m^2). In addition, studies that analysed BMI as a continuous variable were excluded. BMI categories were used as studies in the general population have suggested that the association between BMI and mortality risk is not linear [57]. Thirdly, we attempted to avoid duplication of data in this meta-analysis by excluding studies that had overlapping inclusion dates. However, some overlap may have remained, which could have led to duplication of data. Fourthly, as discussed earlier, there was some evidence of publication bias where it appeared that studies reporting a higher risk of death or likelihood of DGF were more likely to be published. Fifthly, this meta-analysis focussed on a single form of measurement of obesity, i.e. BMI. However, other measures of obesity may also be important. For example, Kovesdy and colleagues investigated the association between waist circumference and mortality [58]. This study demonstrated an association between higher waist circumferences and recipient mortality post-transplantation, which persisted in multivariate analysis. Finally, the studies included in this meta-analysis were all observational in nature, and while there are plausible biological mechanisms by which obesity could affect transplant outcomes, it is possible that other unmeasured confounders may have influenced the results. Ideally, clinical trials investigating the impact of weight loss on transplant outcomes should be performed.

In this meta-analysis, there was no significant difference in the risk of death between obese transplant recipients and those with a normal BMI. This suggests that potential recipients should, therefore, not be excluded from renal transplantation solely on the basis of obesity. However, obese renal transplant recipients had a marginally greater risk of death-censored graft loss and were more likely to develop DGF. There are plausible technical, haemodynamic and immunological explanations for this. Obese renal transplant recipients should have careful optimization prior to surgery to minimize peri-operative morbidity and to reduce the likelihood of additional graft injury.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

JAM is the recipient of a Clinical Research Training Fellowship from Kidney Research UK, and both CH and JAM receive support from the Northern Ireland Kidney Research Fund.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare. The results presented in this article have not been published previously in whole or part, except in abstract form.

REFERENCES

1. Lentine KL, Delos Santos R, Axelrod D *et al.* Obesity and kidney transplant candidates: how big is too big for transplantation? Am J Nephrol 2012; 36: 575–586

2. Friedman AN, Miskulin DC, Rosenberg IH *et al.* Demographics and trends in overweight and obesity in patients at time of kidney transplantation. Am J Kidney Dis 2003; 41: 480–487
3. Yach D, Stuckler D, Brownell KD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. Nat Med 2006; 12: 62–66
4. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; 14: 173–194
5. Hill CJ, Cardwell CR, Maxwell AP *et al.* Obesity and kidney disease in type 1 and 2 diabetes: an analysis of the National Diabetes Audit. QJM 2013; 106: 933–942
6. Luk AOY, So WY, Ma RCW *et al.* Metabolic syndrome predicts new onset of chronic kidney disease in 5,829 Patients with type 2 diabetes—a 5-year prospective analysis of the Hong Kong Diabetes Registry. Diabetes Care 2008; 31: 2357–2361
7. Carrillo A, Ferrer M, Gonzalez-Diaz G *et al.* Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012; 186: 1279–1285
8. Gill JS, Lan J, Dong J *et al.* The survival benefit of kidney transplantation in obese patients. Am J Transplant 2013; 13: 2083–2090
9. Kambham N, Markowitz GS, Valeri AM *et al.* Obesity-related glomerulopathy: An emerging epidemic. Kidney Int 2001; 59: 1498–1509
10. Wuerzner G, Pruijm M, Maillard M *et al.* Marked association between obesity and glomerular hyperfiltration: a cross-sectional study in an African population. Am J Kidney Dis 2010; 56: 303–312
11. Foster MC, Hwang SJ, Larson MG *et al.* Overweight, obesity, and the development of stage 3 CKD: the Framingham heart study. Am J Kidney Dis 2008; 52: 39–48
12. Chagnac A, Herman M, Zingerman B *et al.* Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. Nephrol Dial Transplant 2008; 23: 3946–3952
13. Zimmet P, Alberti K, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414: 782–787
14. Ducloux D, Kazory A, Simula-Faivre D *et al.* One-year post-transplant weight gain is a risk factor for graft loss. Am J Transplant 2005; 5: 2922–2928
15. Afshinnia F, Wilt TJ, Duval S *et al.* Weight loss and proteinuria: systematic review of clinical trials and comparative cohorts. Nephrol Dial Transplant 2010; 25: 1173–1183
16. Khwaja A, El-Nahas M. Transplantation in the obese: separating myth from reality. Nephrol Dial Transplant 2012; 27: 3732–3735
17. Flier S, Knape JTA. How to inform a morbidly obese patient on the specific risk to develop postoperative pulmonary using evidence-based methodology. Eur J Anaesthesiol 2006; 23: 154–159
18. Shabanzadeh DM, Sorensen LT. Laparoscopic surgery compared with open surgery decreases surgical site infection in obese patients a systematic review and meta-analysis. Ann Surg 2012; 256: 934–945
19. Cannon RM, Jones CM, Hughes MG *et al.* The impact of recipient obesity on outcomes after renal transplantation. Ann Surg 2013; 257: 978–984
20. Chang SH, Coates PT, McDonald SP. Effects of body mass index at transplant on outcomes of kidney transplantation. Transplantation 2007; 84: 981–987
21. Lynch RJ, Ranney DN, Shijie C *et al.* Obesity, surgical site infection, and outcome following renal transplantation. Ann Surg 2009; 250: 1014–1020
22. Molnar MZ, Kovesdy CP, Mucsi I *et al.* Higher recipient body mass index is associated with post-transplant delayed kidney graft function. Kidney Int 2011; 80: 218–224
23. Yarlagadda SG, Coca SG, Formica RN *et al.* Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrol Dial Transplant 2009; 24: 1039–1047
24. World Health Organisation. Global Health Observatory. 2013
25. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17: 2815–2834
26. Higgins JP, Thompson SG, Deeks JJ *et al.* Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–560
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–188
28. Aalten J, Christiaans MH, de Fijter H *et al.* The influence of obesity on short- and long-term graft and patient survival after renal transplantation. Transpl Int 2006; 19: 901–907
29. Abou-Jaoude MM, Nawfal N, Najm R *et al.* Effect of pretransplantation body mass index on allograft function and patient survival after renal transplantation. Transplant Proc 2010; 42: 785–788
30. Bardonnaud N, Pillot P, Lillaz J *et al.* Outcomes of renal transplantation in obese recipients. Transplant Proc 2012; 44: 2787–2791
31. Ditonno P, Lucarelli G, Impedovo SV *et al.* Obesity in kidney transplantation affects renal function but not graft and patient survival. Transplant Proc 2011; 43: 367–372
32. Doshi MD, Garg N, Reese PP *et al.* Recipient risk factors associated with delayed graft function: a paired kidney analysis. Transplantation 2011; 91: 666–671
33. Furriel F, Parada B, Campos L *et al.* Pretransplantation overweight and obesity: does it really affect kidney transplantation outcomes? Transplant Proc 2011; 43: 95–99
34. Gore JL, Pham PT, Danovitch GM *et al.* Obesity and outcome following renal transplantation. Am J Transplant 2006; 6: 357–363
35. Grosso G, Corona D, Mistretta A *et al.* The role of obesity in kidney transplantation outcome. Transplant Proc 2012; 44: 1864–1868
36. Halme L, Eklund B, Kyllonen L *et al.* Is obesity still a risk factor in renal transplantation? Transpl Int 1997; 10: 284–288
37. Holley JL, Shapiro R, Lopatin WB *et al.* Obesity as a risk factor following cadaveric renal transplantation. Transplantation 1990; 49: 387–389
38. Hoogeveen EK, Aalten J, Rothman KJ *et al.* Effect of obesity on the outcome of kidney transplantation: a 20-year follow-up. Transplantation 2011; 91: 869–874
39. Modlin CS, Flechner SM, Goormastic M *et al.* Should obese patients lose weight before receiving a kidney transplant? Transplantation 1997; 64: 599–604
40. Singh D, Lawen J, Alkhudair W. Does pretransplant obesity affect the outcome in kidney transplant recipients? Transplant Proc 2005; 37: 717–720
41. Weissenbacher A, Jara M, Ulmer H *et al.* Recipient and donor body mass index as important risk factors for delayed kidney graft function. Transplantation 2012; 93: 524–529
42. Stroup DF, Berlin JA, Morton SC *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012
43. Wells GA, Shea B, O'Connell D *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
44. Flegal KM, Carroll MD, Kit BK *et al.* Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 2012; 307: 491–497
45. Statistics on obesity, physical activity and diet: England, 2013. London, United Kingdom: The Health and Social Care Information Centre, 2013
46. Ferris M, Hogan SL, Chin H *et al.* Obesity, albuminuria, and urinalysis findings in US young adults from the Add Health Wave III study. Clin J Am Soc Nephrol 2007; 2: 1207–1214
47. Shirali AC, Bia MJ. Management of cardiovascular disease in renal transplant recipients. Clin J Am Soc Nephrol 2008; 3: 491–504
48. Kalantar-Zadeh K, Block G, Humphreys MH *et al.* Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int 2003; 63: 793–808
49. Molnar MZ, Streja E, Kovesdy CP *et al.* Associations of body mass index and weight loss with mortality in transplant-waitlisted maintenance hemodialysis patients. Am J Transplant 2011; 11: 725–736
50. Kalantar-Zadeh K, Ikizler TA, Block G *et al.* Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis 2003; 42: 864–881
51. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005; 45: S1–153

52. Chen HM, Liu ZH, Zeng CH *et al*. Podocyte lesions in patients with obesity-related glomerulopathy. Am J Kidney Dis 2006; 48: 772–779
53. Navaneethan SD, Yehnert H, Moustarah F *et al*. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2009; 4: 1565–1574
54. Curran SP, Famure O, Li YH *et al*. Increased recipient body mass index is associated with acute rejection and other adverse outcomes after kidney transplantation. Transplantation 2014; 97: 64–70
55. Espejo B, Torres A, Valentin M *et al*. Obesity favors surgical and infectious complications after renal transplantation. Transplant Proc 2003; 35: 1762–1763
56. Ekberg H, Tedesco-Silva H, Demirbas A *et al*. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007; 357: 2562–2575
57. Flegal KM, Graubard BI, Williamson DF *et al*. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005; 293: 1861–1867
58. Kovesdy CP, Czira ME, Rudas A *et al*. Body mass index, waist circumference and mortality in kidney transplant recipients. Am J Transplant 2010; 10: 2644–2651

Received for publication: 17.12.2014; Accepted in revised form: 15.4.2015