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Research Article

Body Mass Index and Overall Graft Survival: An Analysis of ANZDATA

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Abstract

Obesity is an increasing medical problem across the world and may be associated with adverse renal transplantation outcomes despite contradicting evidences. This retrospective study from 1991 to 2021 using ANZDATA data found that after the initial first 3 years, allografts transplanted to either underweight or obese patients have inferior long-term survival. While weight gain is commonly observed, allografts transplanted to patients who did not gain weight at 3 or 6 months post-transplant fared worse in terms of renal survival. Centers should include baseline body mass index in considering eligibility for renal transplantation.

Keywords: ANZDATA; Graft survival; Obesity; Renal transplantation

Background/Introduction

The epidemic of obesity had spread to the Asian-Pacific world. Sixty-four percent of Australians and New Zealanders were considered as obese (body mass index or BMI≥25kg/m^2) [1]. On the other hand, nearly half of new patients on renal replacement therapy suffered from diabetes [2], that often coexisted with unhealthy lifestyle, lack of exercise and obesity. In fact, the proportion of overweight or obese renal transplant recipients had been increasing [3]. Despite contradicting evidence [4], obese patients suffered more post-surgical complications such as wound infection, lymphocele, perinephric hematoma and incisional hernia after renal transplantation and required longer hospital stay [5,6]. The biggest study to date involved 51927 adult primary renal transplants performed between 1988 and 1997 using USRDS data. Extremes of BMI were associated with inferior graft and patient survival, death-censored graft survival and chronic allograft failure. For BMI above 26kg/m^2, there appeared to be a gradual increase in risk of graft loss as BMI increases [7]. A study based at Australia & New Zealand Dialysis & Transplant Registry (ANZDATA) found obesity to be associated with a higher risk for graft loss and patient death in univariate but not multivariate analysis. Yet, underweight patients had a higher risk for graft loss (especially beyond 5 years) in multivariate analysis despite lower 6-month rejection rates [8]. It is prudent to re-visit the impact of BMI on short and long-term overall graft outcome since variability in the literature was partially accounted by the difference in pre-transplant screening, evaluation and list maintenance [9].

Methods

This was a retrospective cohort study on ANZDATA and included all adult (≥18 years' old) renal transplants performed between 1 January 1991 and 31 December 2012 in Australia and New Zealand. Exclusion criteria included missing data on donor or recipient blood groups and BMI at transplant ≤15kg/m^2 or ≥45kg/m^2. This cohort was categorized into BMI quartiles and followed up for overall graft survival till the end of 2012 or death, whichever was earlier. Continuous data was presented as mean ± standard deviation or median with Interquartile Range (IQR). Group comparisons were calculated by Fisher's exact, Pearson's Chi-square, one-way ANOVA, Student's t or Mann-Whitney U tests whenever appropriate. Kaplan-Meier survival curves were created and groups compared by log-rank test. Multivariate analysis for predictors of overall graft survival was performed by stepwise backward Cox proportional hazards model. Exploratory analyses were performed to see if weight change post-transplant impacted overall graft survivals differently in different baseline BMI quartiles. All p values were two-sided with <0.05 indicating statistically significance. SPSS 20.0 (SPSS Inc., Chicago, IL) was used for all statistical calculations.

Results

A total of 13135 kidney transplants on 12281 patients (7578 male and 4703 female) were enrolled after excluding 1415 allografts according to pre-specified criteria. Patient characteristics were shown in table 1. Over a median follow-up of 6.83 years, female had a lower all-cause mortality (Figure 1) but overall graft survival transplanted to female was not superior (5 years' survival, female: male=81.1% vs. 81.6%; p=0.089).

Recipient and donor characteristics, categorized according to BMI quartiles and defined as underweight, normal, overweight and obesity (Table 2), were tabulated in table 3. In Kaplan-Meier analysis, overall graft survivals diverge significantly after 36 months with allografts transplanted to obese patients survived worst (Figure 2).

This was confirmed in univariate and multivariate analyses which showed BMI having no impact on graft survivals at 1-year, 2-years and 3-years (Table 4). A piecewise multivariate analysis enrolling those 9224 allografts that survived through the first 3 years found

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allografts transplanted to underweight or obese patients to be independently associated within ferior long-term graft survivals, with an adjusted hazards ratio of 1.160 and 1.223, respectively (Table 5).

	Female (n=4703)	Male (n=7578)	All (n=12281)	p
Race				0.000
Caucasoid	3782 (80.4%)	6372 (84.1%)	10154 (82.7%)	
Aboriginal	158 (3.4%)	194 (2.6%)	352 (2.9%)	
Maori	116 (2.5%)	183 (2.4%)	299 (2.4%)	
Indian	93 (2.0%)	196 (2.6%)	289 (2.4%)	
Chinese	92 (2.0%)	125 (1.6%)	217 (1.8%)	
Filipino	115 (2.4%)	65 (0.9%)	180 (1.5%)	
Vietnamese	82 (1.7%)	92 (1.2%)	174 (1.4%)	
Others	265 (5.6%)	351 (4.6%)	616 (5.0%)	
Age (years)	45.99±13.25	46.78±13.03	46.48±13.12	0.001
Weight (kg)	65.70±14.02	79.41±14.89	74.16±16.01	0.000
Height (m)	161.26±8.06	174.40±8.63	169.37±10.57	0.000
BMI (kg/m2)	25.24±4/06	26.06±4.30	25.75±4.58	0.000
Primary renal disease				0.000
Diabetes mellitus	545 (11.6%)	967 (12.8%)	1512 (12.3%)	
Glomerulonephritis	1899 (40.4%)	3797 (50.1%)	5696 (46.4%)	
Polycystic kidney	713 (15.3%)	907 (12.0%)	1620 (13.2%)	
Uncertain	180 (3.8%)	324 (4.3%)	504 (4.1%)	
Others	1366 (28.9%)	1583 (20.8%)	2949 (24.0%)	

Table 1: Patient characteristics at the time of transplant.

Note: BMI=Body Mass Index in kg/m^2.

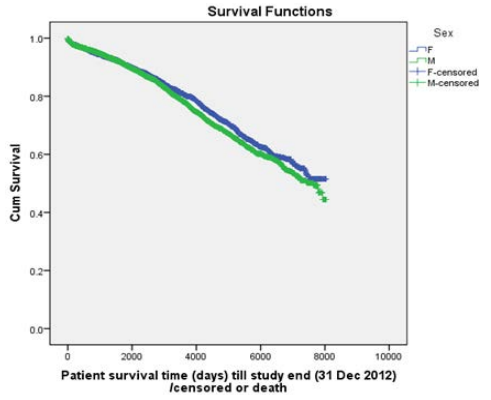

Figure 1: All-cause mortality was slightly lower in female (p=0.022).

An exploratory analysis on 13125 allografts was carried out after excluding allografts that was transplanted to patients with body weight at transplant of ≤35kg or ≥180kg. BMI quartiles (in kg/m^2) were redefined as: <22.40, 22.40-25.21, 25.21-28.63, >28.63. The impact of BMI at transplant on 3-years and long-term graft survivals remained similar. Data on change of body weight post-transplant at 1, 2, 3, 6, 12, 24 and 36 months were available for 12181 allografts. Weight gain post-transplant was common and peaked at 3 months, with a median of +12kg/year (Table 2 and Figure 3).

Quartile	BMI at Transplant	BW Change at 3 Months*	BW Change at 1 Year*	BW Change at 3 Years*
1st(Q1)	<22.39 (Underweight)	->2kg	< 0 kg	<0 kg
2nd (Q2)	22.39-25.21 (Normal)	-2kg to +1kg	+0-4kg	+0-4kg
3rd(Q3)	25.21-28.63 (over-weight)	+1kg to +4kg	+4-8kg	+4-10kg
4th(Q4)	>28.63 (obesity)	+>4kg	+>8kg	+>10kg

Table 2: Derived quartiles of BMI or change of BW at various time points.

Note: BMI=Body Mass Index in kg/m^2; BW=Body Weight in kg.

* when compared with body weight at transplantation.

	Q1 (n=3267)	Q2 (n=3301)	Q3 (n=3286)	Q4 (n=3281)	p
Median (IQR) days of follow-up	2341 (1028-4137)	2284 (980-3869)	2107 (889-3664)	1694 (699-3133)	
Being male	1596 (48.9%)	2146 (65%)	2250 (68.5%)	2109 (64.3%)	0.000
Age	41.42±13.37	45.77±13.01	48.65±12.39	48.99±12.07	0.000
Body weight (kg)	57.58±8.56	69.12±8.76	78.07±9.53	91.11±13.51	0.000
Body height (cm)	167.87±10.36	170.05±10.50	170.43±10.18	168.66±11.75	0.000
BMI (kg/m^2)	20.34±1.51	23.81±0.81	26.79±0.97	31.96±2.92	0.000
CMV seropositive	2126 (65.5%)	2138 (65.1%)	2203 (67.4%)	2279 (69.8%)	0.000
EBV seropositive	2307 (71%)	2338 (71.3%)	2445 (74.8%)	2524 (77.3%)	0.000
Peak panel-reactive antibody					0.001
<25%	2500 (76.5%)	2614 (79.2%)	2654 (80.8%)	2630 (80.2%)	
25-50%	296 (9.1%)	269 (8.1%)	262 (8.0%)	281 (8.6%)	
>50%	459 (14%)	403 (12.2%)	354 (10.8%)	362 (11.0%)	
Repeat transplant	424 (13%)	355 (10.8%)	317 (9.6%)	271 (8.3%)	0.000
ABO incompatible transplant	36 (1.1%)	53 (1.6%)	61 (1.9%)	58 (1.8%)	0.067
Deceased-donor transplant	2085 (63.8%)	2158 (65.4%)	2194 (66.8%)	2221 (67.7%)	0.006
Donor being male	1743 (53.4%)	1703 (51.6%)	1709 (52%)	1757 (53.6%)	0.546
Donor age	42.73±16.09	43.05±16.17	43.85±15.99	44.42±15.67	0.000
Number of HLA (A, B, DR) mismatches					
0	205 (6.3%)	204 (6.2%)	204 (6.2%)	217 (6.6%)	
1	320 (9.8%)	336 (10.2%)	319 (9.7%)	328 (10%)	
2	786 (24.1%)	735 (22.3%)	684 (20.8%)	722 (22%)	
3	770 (23.6%)	669 (20.3%)	715 (21.8%)	629 (19.2%)	
4	479 (14.7%)	541 (16.4%)	514 (15.6%)	543 (16.5%)	
5	479 (14.7%)	557 (16.9%)	561 (17.1%)	550 (16.8%)	
6	228 (7%)	259 (7.8%)	289 (8.8%)	292 (8.9%)	
Ischemic time (hours)	9.71±6.98	9.98±6.91	10.28±7.00	10.30±6.78	0.001

Table 3: Characteristics of renal allografts at transplantation according to BMI quartiles.

Allografts transplanted to patients who did not gain weight or those who lost by more than 2kg at 3 months (or 6 months) post-transplant fared worse in 3 years' (and long-term) survivals (Figure 4). This was observed across all BMI quartiles at transplant. After excluding allografts transplanted to patients with weight loss of more

than 2kg at 3 months (i.e. lowest BW change quartile), survival curves similar to figure 2 was observed, with allografts of obese patients distinctly worse in long-term graft survivals (p by pair wise comparisons<0.014). For patients who were underweight at transplant, gaining more weight at 3 years was associated with improved long-term graft survival. On the other hand, for people with higher BMI, marked weight gain appeared to be increasingly associated with less favourable graft outcome (Figure 5).

Discussion

Obesity was a known risk factor for coronary artery disease, post-transplant diabetes, hyperlipidaemia and pre-transplant or post-transplant hypertension [3,10,11]. Adverse impact of underweight probably partially cancelled out that of obesity, such that inconsistent conclusions been made on the relationship between BMI at transplant and long-term graft outcomes in single-centre studies [12]. Registry studies allowed classifying BMI into multiple categories with adequate number of cases such that a J or U-shaped relationship could be observed [12].

We studied overall graft survival instead of patient or death-censored graft survivals since this outcome provided the best insight to policy makers on whether a certain BMI should deter a patient from receiving a transplant. We found obesity to be associated with more than 20% increased risk of long-term but not short-term (1, 2 or 3 years') overall graft survival. In addition, underweight at transplant increased the risk of long-term graft failure by nearly 16%. This was consistent with the finding of a J-shaped relationship between BMI and graft outcome if BMI at transplant was divided into 11 categories [7].

	Overall Graft Survival (Univariate Analysis)								
	At 1 Year			At 2 Years			At 3 Years		
BMI quartile*	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
1st(Q1)	0.992	0.831-1.183	0.926	1.014	0.867-1.187	0.858	1.043	0.906-1.201	0.554
2nd(Q2)	1			1			1		
3rd (Q3)	0.912	0.762-1.092	0.319	0.983	0.839-1.151	0.829	1.048	0.910-1.207	0.513
4th (Q4)	1.058	0.889-1.259	0.525	1.084	0.929-1.266	0.307	1.090	0.947-1.255	0.230

Table 4: BMI at transplantation did not influence short-term graft survivals.

Note: CI=Confidence Intervals; HR=Unadjusted Hazards Ratio.
*As defined in table 2.

	Allograft Failure at 3 Years			Long-term Allograft Failure		
Multivariate analysis	HR	95% CI	P	HR	95% CI	p
BMI quartiles						
<22.39 (underweight)	1.067	0.922-1.235	0.383	1.158	1.039-1.291	0.008
22.39-25.21 (normal)	1			1		
25.21-28.63 (overweight)	1.024	0.886-1.184	0.744	1.018	0.911-1.138	0.751
>28.63 (obese)	1.054	0.911-1.219	0.479	1.216	1.086-1.361	0.001
Recipient being male	1.001	0.996-1.005	0.790	1.179	1.085-1.281	0.000
Recipient each year older			NA	1.013	1.010-1.017	0.000
DM as primary disease	1.283	1.116-1.476	0.000	1.469	1.311-1.645	0.000
Recipient CMV seropositive	1.156	1.029-1.299	0.015	1.036	0.950-1.129	0.422
Recipient EBV seropositive	0.777	0.664-0.910	0.002			NA
Maximal panel-reactive antibody						
25-50 (c/w <25)	1.334	1.129-1.575	0.001	1.267	1.117-1.437	0.000
>50 (c/w <25)	1.639	1.424-1.888	0.000	1.464	1.303-1.646	0.000
Being a repeat transplant	1.392	1.190-1.628	0.000	1.379	1.209-1.574	0.000
Donor each year older	1.017	1.014-1.020	0.000	1.012	1.009-1.014	0.000
Deceased donor	1.233	1.021-1.488	0.029	1.001	0.861-1.166	0.985
Each HLA-A/B/DR MM	1.096	1.062-1.131	0.000	1.053	1.028-1.079	0.000
Each hr more ischemic time	1.040	1.028-1.051	0.000	1.015	1.009-1.021	0.000
Chronic lung disease	1.270	1.019-1.583	0.034	1.283	1.065-1.545	0.009
Composite CV comorbidities	1.454	1.269-1.667	0.000	1.385	1.235-1.553	0.000

Table 5: Multivariate analyses of the impact of BMI at transplantation on overall graft survival at 3 years and long-term.

Note: CI=Confidence Intervals; CV=Any of the following cardiovascular comorbidities: Cerebrovascular disease, coronary artery disease, peripheral vascular disease; HR=Adjusted hazards ratio in multivariate analysis; NA=Not applicable. The variable was not included in multivariate analysis since it was not statistically significant in univariate analysis.

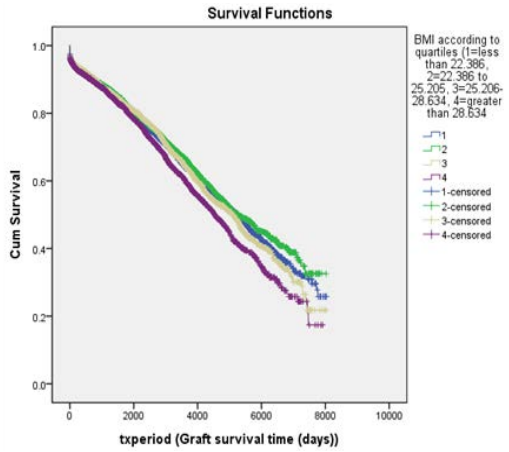

Figure 2: Long-term overall graft survivals according to BMI quartiles.

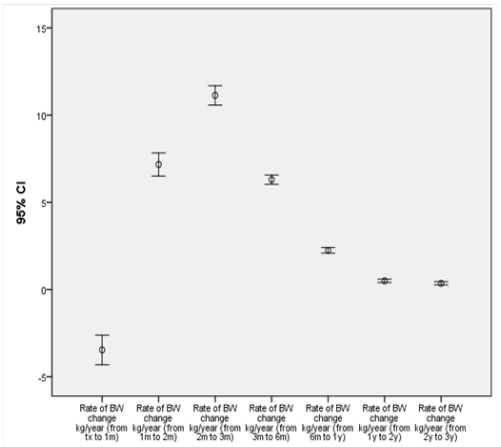

Figure 3: Median (95% confidence intervals) body weight change post-transplant.

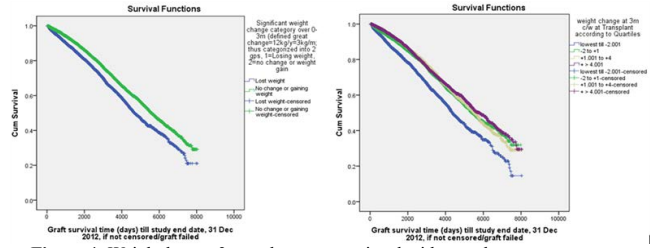

Figure 4: Weight loss at 3 months was associated with poor long-term outcome.

Note: Similar survival curves were obtained in separate analyses using weight change at 6 months as variable or 3-year graft survival as outcome.

The findings were supported by one meta-analysis that showed risk of graft failure in underweight and obese classes to be 1.29 and 1.25, respectively [13]. Difference in enrolment period, primary outcome and definition of underweight or obesity contributed to the variable findings in the literature including a study based at ANZDATA [8].

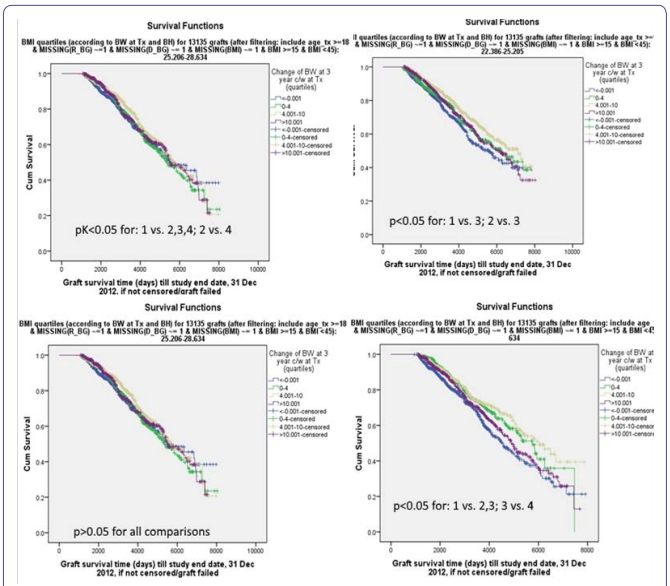

Figure 5: Impact of weight change at 3 years differed for patients with different BMI at transplantation.

Despite contradicting evidence [4,6], obese patients probably carried the same risk of acute rejection [7,9,11], but higher risk of delayed graft function and surgical wound complications [7,12]. It was intriguing to suggest explanations such as inadequate exposure to lipophilic maintenance immunosuppression [14] or inadequate 'nephron dose' in obese recipient [11]. Post-transplant Glomerular Filtration Rate (GFR) at 1 year, as determined by ^{125}I-iothalamate, was higher in the highest BMI tertile [15]. The observation persisted after excluding all diabetic cases which might act as confounder. At 5 years post-transplant, the difference in GFR among BMI groups disappeared, mainly because GFR in the highest BMI tertile dropped when compared with the first year [15]. Nevertheless, given our findings that BMI at transplant never significantly impacted overall graft survival at 1, 2 or 3 years, it was likely that these early complications were mostly manageable or reversible. As such, despite increased surgical difficulties, obesity per se might be considered as one of the adverse risk factors that affect graft and patient outcomes [4]. With paucity supply of organ, setting a specific BMI limit that deter patients from getting a transplant is more than an academic question and complicated by suggestions that relationship between BMI and transplant risk might be continuous [3] and obese patients might be otherwise healthier with more aggressive screening for heart-related problems and closer medical scrutiny [3,16].

Poorer short-term (1 or 5 years') graft survival for underweight patients had been reported [17] and might be explained by the 'carry-over effect' of underweight while on dialysis. Difference in criteria of exclusion of malnourished patients from getting a transplant might explain our finding of no relationship between underweight and short-term graft survival, as similarly reported previously [8]. However, our underweight patients were still at risk of inferior long-term graft survival, with an adjusted odds ratio of 1.158. Chronic calcineurin toxicity due to non weight-adjusted prescription was an intuitive explanation but altered pharmacokinetics, possible predisposition to infections [18] and release of interleukin 2 (IL2) from T cell in reduced energy supply were intriguing factors that promoted development

of chronic allograft nephropathy [19]. Whether matching donor and recipient BMI could benefit the long-term graft outcome remained controversial [9] and we did not have enough data for meaningful analyses. Whatsoever, we might infer that inferior graft outcome in underweight or obese transplant recipients likely involved multiple mechanisms that took time to act.

Allografts transplanted to patients who lost weight by >2kg at 3 months functioned distinctly worse in the long-term. It was likely that these patients either had unmeasured increased risk of transplantation or suffered from post-transplant misfortune or complications including infective or cardiovascular events. In the majority, however, post-transplant weight gain peaked at 3 months and persisted for at least 3 years. In a study enrolling 1000 renal transplant performed on 909 recipients, weight gain at 1 year averaged 5kg or 8.7%. About 50% and 30% of recipients displayed weight gain of 5% and 10%, respectively [12]. Nevertheless, weight gain was not related to baseline BMI [20] and not shown to affect graft or patient outcome [12,15]. In our exploratory analyses, gaining weight (even by>10kg) did not led to poorer graft survival for patients who were underweight at transplant. Yet, despite far from conclusive, our data raised the possibility of adverse impact of persistent huge weight gain at 3 years for obese patients on long-term graft outcome. Obese patients were likely aggressively screened for risk factors before undergoing transplant and thus did well early post-transplant. Obesity and its incident comorbidities, physical inactivity and unhealthy lifestyle likely negatively impacted on graft survival slowly. Since most patients who were obese at transplant were most likely to be obese at 1 or 5 years [8], whether protective weight adjustment before renal transplant could improve graft outcome warrant further studies [7].

As in many retrospective studies, our registry analyses remained mostly descriptive and inspiring rather than allowing confirmation of causal association [21]. We used BMI as the sole definition of obesity or underweight and did not study acute rejection, donor and recipient size mismatch, immunosuppression regime and drug levels [22-30].

In conclusion, underweight (BMI <22.39kg/m^2) and obesity (BMI >28.63) at renal transplant was associated with inferior long-term but not short-term graft survivals. Weight loss at 3 months post-transplant predicted inferior graft outcome while weight gain at 3 years might be problematic in patients who were obese at transplant. Further study of the interplay of weight change post-transplant and baseline BMI is warranted.

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