

Association Between Increased Body Mass Index, Calcineurin Inhibitor Use, and Renal Graft Survival

Nasrollah Ghahramani,¹ W. Brian Reeves,¹ Christopher Hollenbeak^{2,3}

Abstract

Objectives: Using data from the US Renal Data System, we examined the relation between body mass index and graft survival as mediated through calcineurin inhibitor use.

Materials and Methods: Adult patients who received a first kidney-only transplant, with at least 6 months' survival were classified into 5 categories (underweight, normal, overweight, obese, and extremely obese) according to body mass index. Associations between calcineurin inhibitor use, body mass index categories, and outcomes were investigated.

Results: Underweight and normal-weight recipients lived longer than the other 3 categories, regardless of calcineurin inhibitor use. Graft survival was significantly inferior among obese and extremely obese patients. Average graft survival was significantly higher for recipients with a normal body mass index than it was for overweight, obese, and extremely obese recipients. Risk ratio for graft failure was constant for the calcineurin inhibitor versus the noncalcineurin inhibitor group across all body mass index categories. Mean body mass index for the group with rejection episodes was similar to the group with no rejections; there was no correlation between body mass index and rejection risk.

Conclusions: Increased body mass index is associated with inferior patient and graft survival, independent of calcineurin inhibitor use. Because we found no correlation between body mass index and risk of rejection, we assume that, at least after the initial 6 months, the adverse effect of obesity on graft outcome is partially mediated through nonimmunologic mechanisms. When analyzing graft and patient survival rates, we recommend that body mass index be considered a risk factor.

Key words: Kidney, Rejection, Transplant, Weight

Obesity is an independent risk factor for the development of new-onset kidney disease and end-stage renal disease (1-3). Among kidney transplant recipients, a high prevalence of obesity at the time of transplant has been reported (4, 5). In this group, obesity is associated with increased morbidity (6, 7), proteinuria (8), increased risk of delayed graft function, prolonged hospitalization, acute rejection, and decreased graft survival (9-11). Although the direct impact of obesity, independent of associated comorbidities, on graft outcome has been debated (12).

The proposed mechanisms of the effect of obesity on kidney disease include changes in glomerular hemodynamics (13-15), renal fibrosis resulting from the effect of leptin (16), and activation of inflammatory processes (17, 18). The mechanism for inferior graft survival among obese transplant recipients is poorly understood. A possible mechanism is altered metabolism of calcineurin inhibitors (CNIs). Several studies have addressed the effect of body weight on the metabolism and pharmacokinetics of CNI, with conflicting results. While most studies have noted higher cyclosporine levels among obese patients (19-22), 1 study found a lower cyclosporine level among obese patients (23), and several studies have not found

From the Departments of ¹Medicine, ²Surgery, and ³Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania, USA

Acknowledgments: The data reported here have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US Government. This publication was made possible by grant number D1BTH06321-01 from the Office for the Advancement of Telehealth.

Address reprint requests to: Nasrollah Ghahramani, Penn State College of Medicine, Department of Internal Medicine, Division of Nephrology, H040, 500 University Drive, P.O. Box 850, Hershey, PA 17033-085

Phone: +717-531-8156 **Fax:** +717-531-6776 **E-mail:** nghahramani@psu.edu

Experimental and Clinical Transplantation (2008) 3: 199-202

any effect of obesity on cyclosporine metabolism or blood level (24-26). In a study of the relation between cyclosporine dose and the area under the concentration versus time curve, Shibata and associates concluded that there is a nonlinear relation, complicating dosage adjustments in these recipients (27). Whether obesity leads to a higher or a lower cyclosporine level, the study by Shibata and associates raises the possibility that the inability to accurately monitor levels in obese recipients may predispose them to rejection episodes or nephrotoxicity.

Using data from the United States Renal Data System, we examined the relation between BMI at the time of transplant and allograft survival as mediated through CNI use. The goal of our study was to test the hypothesis that there is an adverse effect of BMI on allograft survival, and that this is dependent on the use of CNIs.

Materials and Methods

This is a retrospective cohort study that used data from the United States Renal Data System. We included all adult patients who underwent a first kidney-only transplant between January 1, 1988, and December 31, 1997, and who had at least 6 months of survival. Recipients with a multiorgan transplant or a history of prior renal transplant were excluded. Height and weight recorded at the time of transplant were used to calculate BMI (kg/m^2). Body mass index values were used to classify recipients into the following 5 categories: underweight (< 18.5), normal (18.5 - 24.9), overweight (25 - 29.9), obese (30 - 39.9), and extremely obese (≥ 40). Excluding extreme outlying values (BMI $< 1\%$ and BMI $> 99\%$), 56 988 recipients were identified. The group was further classified into patients who had been discharged on CNIs (CNI group; $n = 52\ 389$) and those who had not (non-CNI group; $n = 4599$) (Table 1).

Table 1. MI and CNI categories.

	CNI	Non-CNI	Total
Underweight	2432	212	2644
Normal	26 532	2309	28 841
Overweight	15 395	1394	16 789
Obese	7627	652	8279
Extremely obese	403	32	435
Total	52 389	4599	56 988

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor.

Statistical analyses

Outcomes of interest were death-censored graft survival and overall patient survival (regardless of

graft function). Using Cox proportional hazard and logistic regression, the independent associations between CNI use, BMI categories, and outcomes were investigated. The model adjusted for potential confounding factors known to affect graft survival such as donor and recipient age, sex, race (white, black, Asian, Native American, or other), ethnicity (Hispanic origin or non-Hispanic origin), donor source, diabetes, number of HLA mismatches, peak panel reactive antibody, induction therapy, underlying renal disease, year of transplant, ischemia times, cytomegalovirus status, and comorbid conditions such as diabetes mellitus and hypertension. The proportional hazard assumption was tested using the log-rank test. Statistical analyses were performed using SAS Software version 9.1 (SAS Institute, Cary, NC).

Results

Long-term patient survival for the 5 BMI categories is illustrated in Table 2. The overweight, obese, and extremely obese recipients displayed inferior survival compared with the normal BMI group at 3 and 5 years. Table 3 illustrates the time from transplant to death among the CNI group and the non-CNI group across the 5 BMI categories. The underweight and normal weight recipients lived longer than did the overweight, obese, and extremely obese recipients ($P < .05$). This was true both for the CNI and the non-CNI groups. Analysis of death-censored graft survival showed significantly inferior outcomes in the obese and extremely obese patients in comparison with those with normal BMIs (Table 4).

Table 2. Patient survival and BMI categories.

BMI category	Percentage patient survival (95% confidence limit)		
	1 Year	3 Years	5 Years
Underweight	98.4 (97.8 - 98.8)	91.6 (90.3 - 92.7)	82.9 (81.0 - 84.7)
Normal	98.6 (98.5 - 98.8)	92.5 (92.2 - 92.9)	83.3 (82.7 - 83.9)
Overweight	98.5 (98.3 - 98.7)	91.3 (90.8 - 91.8)*	80.8 (80.0 - 81.6)*
Obese	98.4 (98.1 - 98.7)	90.2 (89.4 - 91.0)*	77.1 (75.7 - 78.3)*
Extremely obese	97.3 (95.2 - 98.5)	89.8 (85.8 - 92.0)*	76.9 (70.5 - 82.2)*

* $P < .05$ compared with normal BMI.

Abbreviations: BMI, body mass index.

Table 3. Time from transplant to death.

BMI category	Days to death (mean $\pm$ SEM)	
	CNI	Non-CNI
Underweight	2267 $\pm$ 14	2132 $\pm$ 48
Normal	2269 $\pm$ 4	2257 $\pm$ 16
Overweight	2226 $\pm$ 6*	2156 $\pm$ 23*
Obese	2167 $\pm$ 9*	2118 $\pm$ 33*
Extremely obese	2097 $\pm$ 39*	1993 $\pm$ 131*

* $P < .05$ compared with normal BMI.

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor.

This was confirmed by the Cox proportional hazards regression model, which also showed the risk ratio for graft failure to be constant for the CNI versus non-CNI group across all BMI categories (Table 5). Average graft survival was significantly higher for recipients with a normal BMI than it was for overweight, obese, and extremely obese recipients (Table 6). The mean BMI for the group with rejection episodes requiring treatment was similar to the mean BMI for the group with no rejection episode (25.13 ± 4.7 vs 25.13 ± 4.8). There was no correlation between BMI and rejection risk ($P = .19$).

Table 4. Patient survival and BMI categories.

BMI category	Percentage graft survival (95% confidence limit)		
	1 Year	3 Years	5 Years
Underweight	96.6 (95.8 - 97.2)	82.7 (81.0 - 84.2)	66.8 (64.5 - 68.9)
Normal	96.8 (96.6 - 97.0)	84.2 (83.7 - 84.7)	68.9 (68.2 - 69.6)
Overweight	96.5 (96.2 - 96.7)	82.6 (81.9 - 83.7)	66.4 (65.5 - 68.3)
Obese	96.1 (95.7 - 96.5)*	79.2 (78.1 - 80.2)*	60.8 (59.4 - 62.2)*
Extremely obese	94.7 (92.0 - 96.5)*	75.6 (70.5 - 80.0)*	54.2 (47.5 - 60.5)*

* $P < .05$ compared with normal BMI.

Abbreviations: BMI, body mass index.

Table 5. Hazard ratio of graft failure and CNI use.

BMI category	Hazard ratio of failure		Risk ratio (CNI vs non-CNI)
	CNI	Non-CNI	
Underweight	0.86 (0.77-0.97)	0.87 (0.60-1.24)	1.00
Normal	1.00	1.00	1.00
Overweight	1.08 (1.03-1.13)	1.16 (1.01-1.34)	0.93
Obese	1.17 (1.11-1.25)	1.31 (1.09-1.58)	0.89
Extremely obese	1.19 (0.95-1.48)	1.32 (0.65-2.68)	0.90

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor.

Table 6. Time from transplant to death.

BMI category	Days to graft failure (mean $\pm$ SEM)	
	CNI	Non-CNI
Underweight	1991 $\pm$ 17	2006 $\pm$ 59
Normal	2028 $\pm$ 5	2023 $\pm$ 19
Overweight	1988 $\pm$ 7*	1922 $\pm$ 25*
Obese	1885 $\pm$ 11*	1888 $\pm$ 28*
Extremely obese	1778 $\pm$ 47*	1523 $\pm$ 154*

* $P < .05$ compared with normal BMI.

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor.

Discussion

We identified 56 988 patients who had undergone a first kidney-only transplant. A significant number of these patients (4599) had not been discharged on CNIs. In comparing this subset with the group that had been discharged on CNIs and stratifying the patients according to BMI categories, we obtained several findings. We found that obesity was associated with inferior graft and patient survival. This is in agreement

with the results of several other studies that have used large cohorts (9, 10). In a recent study using data from the Australian and New Zealand Dialysis and Transplant Registry, obesity, although associated with factors that led to poorer graft and patient survival, was not by itself associated with poorer kidney transplant outcomes (12). In our study, although diabetes and hypertension were included in the multivariate analysis, underlying cardiovascular disease, which is known to affect survival, was not specifically included. However, the significant differences in death-censored graft survival in the BMI categories suggest that the effect of BMI on graft survival is independent of associated cardiovascular disease. We could not establish a relation between CNI use and the adverse effect of obesity on graft outcome, as indicated by similar risk ratios for graft failure between the CNI and non-CNI group across all BMI categories. The mean BMI of patients with rejection and those without rejection was similar, and there was no correlation between BMI and rejection risk.

Our study is limited by potential selection bias deriving from the fact that obese individuals may have had higher mortality within the initial 6 months and thus not have been included in our study. In addition, obese patients were more likely to have been systematically excluded from transplant by some centers. Another potential source of selection bias may be the underlying reasons that certain patients were not on CNIs. This is not clear from the data source used. In addition, CNI dosing varies among transplant centers, and while many centers have used trough levels, some might have used peak levels. Furthermore, while some centers base dosing on actual body weight, others base it on ideal body weight. The variability of dosing can potentially lead to significant inter- and inpatient variability in CNI exposure.

Other limitations of this study include the inability to differentiate the effects of tacrolimus and cyclosporine and the various formulations of cyclosporine and also, a lack of data on the impact of long-term CNI exposure on the outcomes. Finally, our conclusions are limited by the lack of information on cause of death and also BMI at the time of death. We conclude that among adult first kidney-only recipients, a BMI > 30 is associated with inferior graft and patient survival, and that the adverse effect of obesity on graft outcome is independent of CNI use. Although our study did not specifically monitor immune mediators of graft injury, the finding that

there is no correlation between BMI and risk of rejection implies that at least after the initial 6 months, the adverse effect of obesity on graft outcome is partially mediated through non-immunologic mechanisms. Considering the effect of obesity on graft and patient survival rates, we recommend that in analyses of these rates, BMI should be considered a risk factor. While it is prudent to encourage patients with a BMI over 30 to lose weight before being considered for listing for transplant, it is important not to systematically exclude these patients from transplant until firm data comparing survival of obese patients undergoing dialysis versus transplant become available.

References

1. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology*. 2003 Jul;14(4):479-487.
2. McGovern MP, Fox TS, Xie H, Drake RE. A survey of clinical practices and readiness to adopt evidence-based practices: Dissemination research in an addiction treatment system. *J Subst Abuse Treat*. 2004;26(4):305-312.
3. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Ann Intern Med*. 2006;144(1):21-28.
4. Cofan F, Vela E, Cleries M. Obesity in renal transplantation: analysis of 2691 patients. *Transplant Proc*. 2005;37(9):3695-3697.
5. Friedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity in patients at time of kidney transplantation. *Am J Kidney Dis*. 2003;41(2):480-487.
6. Johnson DW, Isbel NM, Brown AM, et al. The effect of obesity on renal transplant outcomes. *Transplantation*. 2002;74(5):675-681.
7. Massarweh NN, Clayton JL, Mangum CA, Florman SS, Slakey DP. High body mass index and short- and long-term renal allograft survival in adults. *Transplantation*. 2005;80(10):1430-1434.
8. Armstrong KA, Campbell SB, Hawley CM, Nicol DL, Johnson DW, Isbel NM. Obesity is associated with worsening cardiovascular risk factor profiles and proteinuria progression in renal transplant recipients. *Am J Transplant*. 2005;5(11):2710-2718.
9. Gore JL, Pham PT, Danovitch GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, et al. Obesity and outcome following renal transplantation. *Am J Transplant*. 2006;6(2):357-363.
10. Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. *Transplantation*. 2002;73(1):70-74.
11. Raiss-Jalali GA, Mehdizadeh AR, Razmkon A, et al. Effect of body mass index at time of transplantation and weight gain after transplantation on allograft function in kidney transplant recipients in Shiraz. *Transplant Proc*. 2005;37(7):2998-3000.
12. Chang SH, Coates PT, McDonald SP. Effects of body mass index at transplant on outcomes of kidney transplantation. *Transplantation*. 2007;84(8):981-987.
13. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. *Hypertension*. 1995;26(4):610-615.
14. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gaftor U. Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol*. 2000;278(5):F817-822.
15. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol*. 2001;12(6):1211-1217.
16. Wolf G, Chen S, Han DC, Ziyadeh FN. Leptin and renal disease. *Am J Kidney Dis*. 2002;39(1):1-11.
17. Wu Y, Liu Z, Xiang Z, et al. Obesity-related glomerulopathy: insights from gene expression profiles of the glomeruli derived from renal biopsy samples. *Endocrinology*. 2006;147(1):44-50.
18. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003;112(12):1796-1808.
19. Flechner SM, Kolbeinsdottir ME, Tam J, Lum B. The impact of body weight on cyclosporine pharmacokinetics in renal transplant recipients. *Transplantation*. 1989;47(5):806-810.
20. Flechner SM, Haug M, Fisher RK, Modlin CS. Cyclosporine disposition and long-term renal function in a 500-pound kidney transplant recipient. *Am J Kidney Dis*. 1998;32(4):E4.
21. Orofino L, Pascual J, Quereda C, Burgos J, Marcen R, Ortuno J. Influence of overweight on survival of kidney transplant. *Nephrol Dial Transplant*. 1997;12(4):855.
22. Kasap B, Soyulu A, Turkmen M, Kavukcu S, Bora S, Gulay H. Effect of obesity and overweight on cyclosporine blood levels and renal functions in renal adolescent recipients. *Transplant Proc*. 2006;38(2):463-465.
23. Hortal L, Fernandez A, Losada A, et al. Study of the cyclosporine concentration at 2 hours in stable renal transplant patients and relation to body mass index. *Transplant Proc*. 2001;33(7-8):3110-3111.
24. Yee GC, McGuire TR, Gmur DJ, Lennon TP, Deeg HJ. Blood cyclosporine pharmacokinetics in patients undergoing marrow transplantation. Influence of age, obesity, and hematocrit. *Transplantation*. 1988;46(3):399-402.
25. Garcia-Saiz M, Lopez-Gil A, Alfonso I, Boada JN, Armijo JA. Factors influencing cyclosporine blood concentration-dose ratio. *Ann Pharmacother*. 2002;36(2):193-199.
26. Modlin CS, Flechner SM, Goormastic M, et al. Should obese patients lose weight before receiving a kidney transplant? *Transplantation*. 1997;64(4):599-604.
27. Shibata N, Hoshino N, Minouchi T, et al. Relationship between area under the concentration versus time curve of cyclosporin A, creatinine clearance, hematocrit value, and other clinical factors in Japanese renal transplant patients. *Int J Clin Pharmacol Ther*. 1998;36(4):202-209.