Impact of High Body Mass Index on The Allograft Outcomes in Kidney Transplant Recipients with Pre-Sensitization to Human Leukocyte Antigen: A Retrospective Cohort Study

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Abstract

Background The aim of this study was to investigate whether high body mass index (BMI) and pre-sensitization to human leukocyte antigen (HLA) in kidney transplant recipients (KTR) had a synergistic impact on the allograft outcomes.

Methods From January 2010 to December 2018, 1,290 KT were performed in Seoul St Mary's Hospital. Of these, 682 cases of ABO compatible KT were enrolled. They were divided into 4 groups (low BMI-non-sensitized, high BMI-non-sensitized, low BMI sensitized, high BMI-sensitized) according to the median BMI value (22.7 kg/m^2) and HLA pre-sensitization status (HLA-DSA MFI $>3,000$). Short-term and long-term allograft outcomes were compared between the groups.

Results The rate of late antibody mediated rejection tended to be the highest in the high BMI-sensitized group, and the decline in allograft function in the high BMI-sensitized group was higher than in the other 3 groups. Death-censored graft loss (DCGL) rates and the hazard ratio (HR) for DCGL were the highest in the high BMI-sensitized group (4/21 (19.0%), HR 4.648, $P = 0.022$) and a significant interaction was detected between high BMI and HLA pre-sensitization status (P value for interaction = 0.008).

Conclusions Our results suggest that pre-sensitization to HLA and high BMI in KTRs might have a synergistic adverse impact on the allograft outcomes.

Background

Obesity is a major public health problem that is increasing worldwide [1], and its prevalence in Korea has increased from 29.2% in 2001 to 34.6% in 2018 [2]. Obesity and metabolic syndrome are recognized as risk factors for the development and progression of chronic kidney disease (CKD) through various mechanisms [3, 4]. In a previous nationwide cohort study in Korea, obesity (body mass index (BMI) $\geq 25 \text{ kg/m}^2$) was identified as an independent risk factor for the progression of CKD [5]. Moreover, obesity also adversely affects the allograft function in kidney transplant (KT) recipients. A previous study reported that BMI $\geq 35 \text{ kg/m}^2$ was an independent risk factor for death-censored graft loss (DCGL) and biopsy-proven acute rejection (BPAR) (hazard ratio (HR) 2.43 (95% confidence interval (CI), 1.48–3.99), HR 2.43 (95% CI, 1.07–5.51), respectively) [6]. Another previous study also reported that BMI $\geq 35 \text{ kg/m}^2$ was an independent risk factor for overall graft loss (HR 1.22; 95% CI, 1.09–1.38) [7]. A meta-analysis also reported that recipient obesity had a marginally greater risk for DCGL (HR 1.06; 95% CI, 1.01–1.12) [8].

Meanwhile, pre-transplant sensitization to human leukocyte antigen (HLA) is a well-known risk factor associated with adverse allograft outcomes [9]. Pre-sensitization to HLA is not only associated with a high rate of acute antibody mediated rejection (ABMR), but also with the gradual development of chronic allograft tissue injury caused by activation of the humoral immune system. Indeed, the development of chronic antibody mediated rejection (cAMR) was significantly higher in patients with pre-sensitization to HLA compared to patients with low immunologic risk [10–12]. In addition, both pre-formed persistent

donor specific antibody (DSA) and pre-formed cleared DSA showed an increased risk of graft loss [9]. Another previous study also reported that preformed donor specific anti-human leukocyte antigen antibody (HLA-DSA) with mean fluorescence intensity (MFI) > 3000 had an increased risk for graft loss with a HR of 3.8 (P < 0.001) [13].

Therefore, both obesity and pre-transplant sensitization to HLA in recipients might contribute to the progression of chronic allograft tissue injury and adverse allograft outcomes, although the mechanisms are different. However, it has not been investigated whether both factors have a synergistic effect on allograft outcomes. Hence, we analyzed the short-term and long-term graft outcomes in kidney transplant recipients (KTRs) with high BMI and pre-sensitization to HLA, and investigated the interaction between high BMI and HLA pre-sensitization status in this study

Methods

Study Design

This study was a retrospective, observational and single-center study. Between January 2010 and December 2018, 1290 KT were performed in Seoul St. Mary's Hospital. Of these, 412 cases received the kidney from a deceased donor, 195 cases were ABO incompatible KT, and 1 KTR had both legs amputated; these cases were excluded from the study. Finally, 682 KTRs were included in this analysis. The distribution of BMI of the KTRs is presented in Supplemental Figure S1 and the median BMI value was 22.7 kg/m². Patients with BMI >22.7 kg/m² were categorized in the high BMI group, while others were classified in the low BMI group. The cases were defined as pre-sensitized to HLA when the MFI value of HLA-DSA at baseline was higher than 3,000 [13] while if the value was below 3,000, they were defined as non-sensitized. Based on the above classifications, KTRs were divided into 4 groups (low BMI-non-sensitized, high BMI-non-sensitized, low BMI-sensitized, high BMI-sensitized) as presented in Figure 1. This study followed the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul St. Mary's Hospital (XC15RIMI0072K).

HLA Typing, HLA Antibodies, and DSA

HLA typing and HLA antibodies were measured as described previously [14, 15]. Briefly, HLA-A, B, DR, DQB1 typing was performed using the deoxyribonucleic acid molecular typing method using sequence-specific oligonucleotide probes with LIFECODES HLA SSO typing kits (Immucor, Stamford, CT). Lifecodes LSA Class I and Class II kits (Gen-Probe Transplant Diagnostic Inc., Stamford, CT) or LABScreen Single Antigen (One Lambda Inc., A Thermo Fisher Scientific Brand, Canoga Park, CA) were used for detecting HLA antibodies in the recipient sera. According to the manufacturer's instructions, 10 µL of each serum sample was used, and the fluorescence intensities of the samples were measured using a Luminex 200 system (Luminex Corp., Austin, TX).

Desensitization Protocols for Pre-sensitized Patients

The desensitization protocol in our center has been described previously [16-18]. Briefly, the desensitization protocol for HLA pre-sensitized patients consisted of rituximab, total plasma exchange (TPE) and intravenous immunoglobulin (IVIG). Two weeks to one month prior to the transplantation, rituximab was administered, and total plasma exchange using 5% albumin and fresh frozen plasma was performed seven times. The TPE frequency was controlled based on the MFI titer of HLA-DSA. IVIG was administered at a dose of 100 mg/kg over a period of 1 hour after every TPE. In all patients who underwent desensitization, prophylactic agents were used to prevent pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) infection. If the crossmatch (XM) test of T-cell complement dependent cytotoxicity (CDC) was positive or HLA-DSA was positive, and the MFI of HLA-DSA did not decrease adequately after 3 cycles of TPE, bortezomib based protocol was used, in which bortezomib was administered for four times in addition to the desensitization protocol.

Clinical Parameters and Outcomes

KTRs' age, height, weight, history of diabetes mellitus (DM) and hypertension (HTN), cause of end stage renal disease (ESRD), previous dialysis modality, previous dialysis period, and previous KT history were collected as baseline demographic characteristics. In addition, fasting glucose, total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, and hemoglobin A1c levels were obtained from the pre-transplant investigations. As a pre-transplant immunoassay, the results of XM test using CDC and flow cytometry-crossmatch (FCXM), HLA-DSA and MFI results by Luminex Single Antigen Assay, and panel reactive antibody (PRA) titers were obtained. Transplantation information was collected for mismatch number, type of induction therapy, main immunosuppressant used, and drug used for desensitization.

We analyzed the incidence of BPAR within 1-year of transplantation (early acute rejection), CMV infection, BK viremia, and PJP rates as short-term clinical outcomes in the 4 groups. The variables used for analyzing long-term clinical outcomes comprised BPAR incidence after 1-year of transplantation (late acute rejection), cAMR, and biopsy-proven calcineurin inhibitor (CNI) toxicity rates. DCGL and patient death rates were also analyzed.

Allograft kidney biopsy findings were interpreted according to Banff classification 2009. BPAR was diagnosed with allograft biopsy as suitable for acute T-cell mediated rejection (TCMR) and acute ABMR criteria according to Banff classification. Similarly, cAMR and biopsy proven CNI toxicity were diagnosed with allograft biopsies according to the Banff classification [19]. Death-censored allograft survival duration was defined as the period from KT to dialysis or preemptive KT, except for patient death in a functioning allograft. Patient survival duration was defined as the period from KT to death due to any cause. Data of changes in allograft function based on serum creatinine levels was collected until 4 years after KT.

The primary outcome of this study was to compare the impact of BMI on DCGL in HLA non-sensitized and sensitized patients. We compared the DCGL rate and death censored allograft survival duration in the 4 groups and analyzed the interaction between high BMI and HLA pre-sensitization status. Secondary

outcomes of this study were early acute rejection, CMV infection, BK viremia, PJP, late acute rejection, cAMR, biopsy proven CNl toxicity, patient death rates, and estimated glomerular filtration rate (eGFR) based on Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation [20].

Statistical Analysis

All continuous variables were expressed as mean $\pm$ standard deviation. If the variables followed the normal distribution, an analysis of variance (ANOVA) test was performed. If the variables showed non-normal distribution, a Kruskal-Wallis test was performed. All categorical variables were compared using the chi-square test or Fisher's exact test and expressed as proportions. Multivariate Cox hazard regression model analysis was performed to determine the risk factors affecting DCGL and to investigate the interaction between high BMI and HLA pre-sensitization. Cumulative survival rates were analyzed during the follow-up period in the 4 groups. Causes of DCGL and patient death were compared using the chi-square test or Fisher's exact test. The mean eGFR (CKD-EPI) and standard deviation in the 4 groups were evaluated. All statistical analyses were performed using the SPSS[®] software, version 24 (IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2016.

Results

Comparison of baseline clinical and laboratory parameters in the 4 groups according to BMI and HLA pre-sensitization status

The mean follow-up duration of the patients included in this study was 61.8 months. The baseline characteristics of the 4 groups are shown in Table 1. In terms of clinical demographics, the age at KT was significantly lower in the low BMI-non-sensitized group (44.8 years, $P < 0.001$, for all), and the proportion of male patients was higher in the non-sensitized groups, especially in the high BMI-non-sensitized group (235/319, 73.7%, $P < 0.001$). Average BMI and the percentage of patients with DM and HTN were higher in the high BMI groups than in the low BMI groups ($P < 0.001$). Mean fasting glucose, triglyceride level, and hemoglobin A1c level was significantly higher ($P < 0.001$, $P = 0.001$, and $P < 0.001$, for all), and HDL-cholesterol level was lower in both high BMI groups ($P < 0.001$, for each) compared to that in the low BMI groups. Percentage of patients with previous KT history was highest in the low BMI-sensitized group (13/40, 32.5%, $P < 0.001$), and the percentage of patients in whom DM was the cause of ESRD was significantly higher in both high BMI groups ($P < 0.001$). Of the types of dialysis modality, the percentage of peritoneal dialysis was highest in the high BMI-non-sensitized group (47/319, 14.7%, $P = 0.016$).

Table 1
Comparison of baseline characteristics the 4 groups according to BMI and pre-sensitization status

	Low BMI- non- sensitized (n = 302)	High BMI- non- sensitized (n = 319)	Low BMI- sensitized (n = 40)	High BMI- sensitized (n = 21)	P- value
Age (years)	44.8 ± 12.6 ^{†‡§}	50.6 ± 11.2 [*]	50.2 ± 6.1 ^{*§}	55.4 ± 9.0 ^{*‡}	< 0.001
Male	138 (45.7%) ^{†‡}	235 (73.7%) ^{*‡§}	10 (25.0%) ^{*†}	5 (23.8%) [†]	< 0.001
BMI (kg/m ²)	20.2 ± 1.8 ^{†§}	25.9 ± 2.7 ^{*‡}	20.4 ± 1.6 ^{†§}	24.7 ± 1.7 ^{*‡}	< 0.001
DM	48 (15.9%) ^{†§}	115 (36.1%) ^{*‡}	7 (17.5%) ^{†§}	9 (42.9%) ^{*‡}	< 0.001
HTN	176 (58.3%) [†]	237 (74.3%) ^{*‡}	18 (45.0%) [†]	14 (66.7%)	< 0.001
Fasting glucose (mg/dL)	100.1 ± 43.0 ^{†‡}	106.1 ± 37.6 ^{*‡}	90.4 ± 24.0 ^{*†§}	103.2 ± 29.6 [‡]	< 0.001
Total cholesterol (mg/dL)	163.2 ± 52.8	156.0 ± 43.1	161.9 ± 40.0	156.2 ± 42.7	0.299
Triglyceride (mg/dL)	120.5 ± 67.7 [†]	148.9 ± 91.3 ^{*‡}	119.3 ± 65.1 [†]	147.6 ± 84.7	0.001
HDL-cholesterol (mg/dL)	47.0 ± 16.4 ^{†§}	37.4 ± 12.1 ^{*‡}	44.2 ± 11.3 [†]	38.2 ± 10.0 [*]	< 0.001
LDL-cholesterol (mg/dL)	85.7 ± 35.2	85.1 ± 32.6	84.4 ± 30.0	79.9 ± 29.5	0.955
Hemoglobin A1c (%)	5.4 ± 0.9 ^{†§}	5.8 ± 1.1 ^{*‡}	5.4 ± 1.2 ^{†§}	6.1 ± 1.4 ^{*‡}	< 0.001
Previous KT history	36 (11.9%) ^{†‡}	21 (6.6%) ^{*‡}	13 (32.5%) ^{*†}	3 (14.3%)	< 0.001
Dialysis vintage (months)	18.2 ± 33.7	16.6 ± 25.7	28.2 ± 46.9	12.3 ± 17.1	0.558

Continuous variables are shown as mean ± standard deviation and categorical variables are shown as proportions. * P < 0.05 versus low BMI-non-sensitized group, † P < 0.05 versus high BMI-non-sensitized group, ‡ P < 0.05 versus low BMI-sensitized group, § P < 0.05 versus high BMI-sensitized group.

BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, HDL: high-density lipoprotein, LDL: low-density lipoprotein, KT: kidney transplantation, ESRD: end stage renal disease, CGN: clinical glomerulonephritis, DSA: donor specific antibody, MFI: mean fluorescence intensity

	Low BMI- non- sensitized (n = 302)	High BMI- non- sensitized (n = 319)	Low BMI- sensitized (n = 40)	High BMI- sensitized (n = 21)	P- value
Cause of ESRD					
DM	36 (11.9%) ^{†§}	100 (31.3%) ^{*‡}	4 (10.0%) ^{†§}	8 (38.1%) ^{*‡}	< 0.001
HTN	21 (7.0%)	38 (11.9%)	2 (5.0%)	2 (9.5%)	0.141
CGN	123 (40.7%) [†]	91 (28.5%) [*]	14 (35.0%)	7 (33.3%)	0.017
Others	122 (40.4%) [†]	90 (28.2%) ^{*‡}	20 (50.0%) ^{†§}	4 (19.0%) [‡]	0.001
Dialysis modality					
Hemodialysis	185 (61.3%) [†]	160 (50.2%) [*]	24 (60.0%)	13 (61.9%)	0.039
Peritoneal dialysis	22 (7.3%) [†]	47 (14.7%) [*]	3 (7.5%)	1 (4.8%)	0.016
Preemptive transplantation	95 (31.5%)	112 (35.1%)	13 (32.5%)	7 (33.3%)	0.815
Pre-sensitization status					
Crossmatch positive	18 (6.0%) ^{‡§}	7 (2.2%) ^{‡§}	20 (50.0%) ^{*†}	10 (47.6%) ^{*†}	< 0.001
DSA (Any titer)	20 (6.6%) ^{‡§}	16 (5.0%) ^{‡§}	40 (100.0%) ^{*†}	21 (100.0%) ^{*†}	< 0.001
DSA (MFI ≥ 3000)	0 (0%) ^{‡§}	0 (0%) ^{‡§}	40 (100.0%) ^{*†}	21 (100.0%) ^{*†}	< 0.001
PRA > 50%	65 (21.5%) ^{‡§}	57 (17.9%) ^{‡§}	36 (90.0%) ^{*†}	17 (81.0%) ^{*†}	< 0.001
Mismatch number	2.9 ± 1.7	3.2 ± 1.7	3.4 ± 1.4	3.4 ± 1.4	0.051
Induction therapy					

Continuous variables are shown as mean ± standard deviation and categorical variables are shown as proportions. * P < 0.05 versus low BMI-non-sensitized group, † P < 0.05 versus high BMI-non-sensitized group, ‡ P < 0.05 versus low BMI-sensitized group, § P < 0.05 versus high BMI-sensitized group.

BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, HDL: high-density lipoprotein, LDL: low-density lipoprotein, KT: kidney transplantation, ESRD: end stage renal disease, CGN: clinical glomerulonephritis, DSA: donor specific antibody, MFI: mean fluorescence intensity

	Low BMI- non- sensitized (n = 302)	High BMI- non- sensitized (n = 319)	Low BMI- sensitized (n = 40)	High BMI- sensitized (n = 21)	P- value
Basiliximab	279 (92.4%) ^{‡§}	291 (91.2%) ^{‡§}	19 (47.5%) ^{*†}	8 (38.1%) ^{*†}	< 0.001
Antithymocyte globulin	23 (7.6%) ^{‡§}	28 (8.8%) ^{‡§}	21 (52.5%) ^{*†}	13 (61.9%) ^{*†}	< 0.001
Immunosuppressant					
Tacrolimus	287 (95.0%)	304 (95.3%)	39 (97.5%)	21 (100.0%)	0.676
Cyclosporin	15 (5.0%)	15 (4.7%)	1 (2.5%)	0 (0%)	0.676
Desensitization therapy					
Rituximab	63 (20.9%) ^{‡§}	50 (15.7%) ^{‡§}	36 (90.0%) ^{*†}	19 (90.5%) ^{*†}	< 0.001
Bortezomib	0 (0%) [‡]	0 (0%) [‡]	3 (7.5%) ^{*†}	1 (4.8%)	< 0.001
Continuous variables are shown as mean ± standard deviation and categorical variables are shown as proportions. * P < 0.05 versus low BMI-non-sensitized group, † P < 0.05 versus high BMI-non-sensitized group, ‡ P < 0.05 versus low BMI-sensitized group, § P < 0.05 versus high BMI-sensitized group.					
BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, HDL: high-density lipoprotein, LDL: low-density lipoprotein, KT: kidney transplantation, ESRD: end stage renal disease, CGN: clinical glomerulonephritis, DSA: donor specific antibody, MFI: mean fluorescence intensity					

In the baseline immunologic test, the number of patients with positive XM test was significantly higher in the HLA sensitized groups than in the non-sensitized groups ($P < 0.001$); however, no difference in the rate of positivity was seen between patients with low BMI and high BMI within the HLA sensitized groups ($P = 0.396$). Use of anti-thymocyte globulin as induction therapy and percentage of desensitization therapy were significantly higher in the HLA sensitized groups compared to that in the non-sensitized groups ($P < 0.001$, for each).

Comparison of the short-term clinical outcomes, long-term clinical outcomes, and allograft functions among the 4 groups according to BMI and pre-sensitization status

Table 2 shows the short-term and long-term clinical outcomes in the 4 groups. In the short-term clinical outcomes, the rate of early ABMR was significantly higher in the HLA sensitized groups ($P < 0.001$) but there was no significant difference between those with low and high BMI within the sensitized groups. CMV infection and BK viremia rates tended to be higher in the HLA sensitized groups; however, the difference was not significant ($P = 0.110$, $P = 0.208$, respectively). Early TCMR and PJP rates did not show

statistically significant differences between the 4 groups ($P = 0.458$). In long-term clinical outcomes, the rate of late ABMR tended to be highest in the high BMI-sensitized group although the difference was not significant (2/21, 9.5%, $P = 0.154$). There were no significant differences in the rates of late TCMR, cAMR, and biopsy-proven CNI toxicity between the 4 groups.

Table 2
Comparison of short-term and long-term clinical outcomes among the 4 groups according to BMI and pre-sensitization status

	Low BMI- non- sensitized (n = 302)	High BMI- non- sensitized (n = 319)	Low BMI- sensitized (n = 40)	High BMI- sensitized (n = 21)	P-value
Short-term outcomes					
Early ABMR	13 (4.3%) ^{‡§}	12 (3.8%) ^{‡§}	16 (40.0%) ^{*†}	6 (28.6%) ^{*†}	< 0.001
Early TCMR	32 (10.6%)	47 (14.7%)	4 (10.0%)	1 (4.8%)	0.277
CMV infection	36 (11.9%)	35 (11.0%)	6 (15.0%)	6 (28.6%)	0.110
BK viremia	44 (14.6%)	40 (12.5%)	9 (22.5%)	5 (23.8%)	0.208
PJP	3 (1.0%)	7 (2.2%)	1 (2.5%)	1 (4.8%)	0.458
Long-term outcomes					
Late ABMR	6 (2.0%)	8 (2.5%)	2 (5.0%)	2 (9.5%)	0.154
Late TCMR	13 (4.3%)	9 (2.8%)	2 (5.0%)	1 (4.8%)	0.737
Chronic ABMR	4 (1.3%)	13 (4.1%)	1 (2.5%)	1 (4.8%)	0.199
Biopsy-proven CNI toxicity	18 (6.0%)	23 (7.2%)	1 (2.5%)	1 (4.8%)	0.667
Categorical variables are shown as proportions. * $P < 0.05$ versus low BMI-non-sensitized group, † $P < 0.05$ versus high BMI-non-sensitized group, ‡ $P < 0.05$ versus low BMI-sensitized group, § $P < 0.05$ versus high BMI-sensitized group.					
BMI: body mass index, ABMR: acute antibody mediated rejection, TCMR: T-cell mediated rejection, CMV: cytomegalovirus, PJP: pneumocystis jiroveci pneumonia, CNI: calcineurin inhibitor					

Figure 2 shows the change in mean eGFR during the follow-up period after transplantation in the 4 groups. Although eGFR did not show statistically significant differences between the 4 groups, the decline in eGFR was higher in the high BMI-sensitized group compared to that in the other 3 groups after 1 year of KT. Moreover, in this group the eGFR was less than 60 ml/min/1.73 m² after 3 years of KT, while it was more than 60 ml/min/1.73 m² in the other 3 groups after 4 years of KT.

Comparison of DCGL rate and its causes in the 4 groups according to BMI and pre-sensitization status

In all, 44 DCGL events occurred; of these, 14 were in the low BMI-non-sensitized group (14/302, 4.6%), 22 in the high BMI-non-sensitized group (22/319, 6.9%), and 4 each in the low BMI-sensitized group (4/40, 10.0%), and high BMI-sensitized group (4/21, 19.0%) (Table 3). There were no statistically significant differences in the causes of DCGL between the 4 groups. In the cumulative death-censored allograft survival rate curve, the graft survival rate decreased significantly in the sensitized groups and it was poorest in the high BMI-sensitized group (Fig. 3). Multivariate Cox hazard regression model analysis showed that low BMI-sensitized status (adjusted HR 3.377, 95% CI, 1.082–10.538, $P = 0.036$) and high BMI-sensitized status (adjusted HR 4.648, 95% CI 1.251–17.276, $P = 0.022$) were independent risk factors for DCGL after adjustment for the factors which were shown statistical differences in baseline characteristics; age, sex, DM, HTN, fasting glucose, triglyceride, HDL-cholesterol, hemoglobin A1c, cause of ESRD, dialysis modality, and previous KT history. Furthermore, high BMI and HLA pre-sensitization showed statistically significant interactions for DCGL (P -value for interaction = 0.008) (Table 5).

Table 3

Comparison of death-censored graft loss and patient death rates among the 4 groups according to BMI and pre-sensitization status

	Low BMI- non-sensitized (n = 302)	High BMI- non-sensitized (n = 319)	Low BMI- sensitized (n = 40)	High BMI- sensitized (n = 21)	P-value
Death censored graft loss	14 (4.6%) [§]	22 (6.9%)	4 (10.0%)	4 (19.0%)*	0.044
Patient death	8 (2.6%)	12 (3.8%)	1 (2.5%)	0 (0%)	0.706
Categorical variables are shown as proportions. * $P < 0.05$ versus low BMI-non-sensitized group, [†] $P < 0.05$ versus high BMI-non-sensitized group, [‡] $P < 0.05$ versus low BMI-sensitized group, [§] $P < 0.05$ versus high BMI-sensitized group.					
BMI: body mass index					

Table 4

Comparison of the causes of graft loss and patient death among the 4 groups according to BMI and pre-sensitization status

	Low BMI- non- sensitized (n = 14)	High BMI- non- sensitized (n = 22)	Low BMI- sensitized (n = 4)	High BMI- sensitized (n = 4)	P-value
Causes of graft loss					
Acute rejection	3 (14.3%)	7 (31.8%)	2 (50.0%)	2 (50.0%)	0.328
Chronic active TCMR/ABMR	2 (14.3%)	4 (18.2%)	0 (0%)	1 (25.0%)	0.773
BKVN	1 (7.1%)	1 (4.5%)	0 (0%)	1 (25.0%)	0.465
Recurrent glomerulonephritis	3 (21.4%)	1 (4.5%)	0 (0%)	0 (0%)	0.269
Others	2 (14.3%)*	4 (18.2%) [†]	2 (50.0%) [‡]	0 (0%)	0.289
Unknown	4 (28.6%)	5 (22.7%)	0 (0%)	0 (0%)	0.441
	Low BMI- non- sensitized (n = 8)	High BMI- non- sensitized (n = 12)	Low BMI- sensitized (n = 1)	High BMI- sensitized (n = 0)	P-value
Causes of patient death					
Cardiac	1 (12.5%)	2 (16.7%)	0 (0%)	0 (0%)	0.886
Pulmonary	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	0.675
Vascular	0 (0%)	2 (16.7%)	0 (0%)	0 (0%)	0.437
Infection	4 (50.0%)	3 (25.0%)	1 (100.0%)	0 (0%)	0.226
Malignancy	3 (37.5%)	3 (25.0%)	0 (0%)	0 (0%)	0.675
Unknown	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	0.675
Categorical variables are shown as proportions. *Graft loss causes of others were postoperative bleeding and amyloidosis. [†] Graft loss causes of others were drug-induced nephropathy, sepsis, oxalate nephropathy and thrombotic microangiopathy. [‡] Graft loss causes of others were 2 cases of postoperative bleeding.					
BMI: body mass index, TCMR: T-cell mediated rejection, ABMR: antibody mediated rejection, BKVN: BK virus associated nephropathy					

Table 5
Hazard ratios of death-censored graft loss according to BMI and pre-sensitization status

	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)*	P-value	P-value for interaction
Low BMI- non-sensitized	Reference		Reference		0.008
High BMI- non-sensitized	1.661 (0.849–3.247)	0.138	1.495 (0.735–3.041)	0.267	
Low BMI- sensitized	2.650 (0.872–8.057)	0.086	3.377 (1.082–10.538)	0.036	
High BMI- sensitized	5.656 (1.859–17.211)	0.002	4.648 (1.251–17.276)	0.022	
*Multivariate regression model was adjusted with parameters showing significant difference among the 4 groups according to BMI and pre-sensitization status. Parameters were as follows: Age, Sex, DM, HTN, Fasting glucose, Triglyceride, HDL-cholesterol, Hemoglobin A1c, ESRD causes, Dialysis modality, and Prior KT history.					
HR: hazard ratio, CI: confidence interval, BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, HDL: high density lipoprotein, ESRD: end stage renal disease, KT: kidney transplantation					

Comparison of patient death rate and its causes in the 4 groups according to BMI and pre-sensitization status

In all 21 patients died; however, there was no significant difference in the rate of death between the 4 groups; 8 deaths occurred in the low BMI-non-sensitized group (8/302, 2.6%), 12 in the high BMI-non-sensitized group (12/319, 3.8%), 1 in the low BMI-sensitized group (1/40, 2.5%), and no patient death occurred in the high BMI-sensitized group (Table 3). When comparing the causes of death between the groups, there were no significant differences (Table 4).

Discussion

In this study, we analyzed the short-term and long-term allograft outcomes according to high BMI and HLA pre-sensitization status of the recipients. We found that the high BMI-sensitized group showed the most significant decline in allograft function among 4 groups, and had the highest DCGL rates. In addition, high BMI-sensitized status was found to be an independent risk factor for DCGL. There was also a significant interaction between high BMI and pre-transplant HLA sensitivity. Our results suggest that increased immunologic risk and high BMI might induce synergistic effects leading to adverse allograft outcomes.

We divided the high BMI and low BMI groups based on the median BMI value of 22.7 kg/m² of the patients included in this study. According to the World Health Organization's International Obesity Task Force recommendation, when analyzing co-morbidities risk, the Asian population sets the BMI value of obesity to 25 kg/m² and the BMI value of overweight to 23 kg/m² [21]. The median BMI value in this study, 22.7 kg/m², was approximately close to the Asian population overweight cutoff value, and most patients in the high BMI group met the Asian overweight criteria.

In the comparison of baseline characteristics, the rates of DM and HTN as a comorbidity were higher in the high BMI groups, and laboratory parameters such as fasting glucose, triglyceride, HDL-cholesterol, and hemoglobin A1c also showed suitable differences as metabolic syndrome as expected [22]. As previously reported, the rate of previous KT history was higher in the sensitized groups [23]. Lastly, the rate of peritoneal dialysis prior to transplantation was significantly higher in the high BMI group than in the low BMI group. It is thought that weight gain occurs due to glucose absorption from the peritoneal dialysate in patients undergoing peritoneal dialysis [24].

In the comparison of short-term outcomes, the rates of CMV infection and BK viremia tended to be higher in the HLA pre-sensitized groups. These could be due to immunosuppression caused by desensitization therapy despite adequate prophylaxis in the sensitized groups. In a nationwide cohort study in Korea, which we published previously, desensitization therapy has also been found to be a significant risk factor for infection related mortality [25]. Early ABMR rates were higher in the HLA pre-sensitized groups, and the rates of late ABMR also tended to be higher in the sensitized groups. These results were consistent with previous studies, which showed that acute rejection rate is higher despite appropriate desensitization therapy in those with HLA pre-sensitization [17, 25].

In the comparison of long-term outcomes, a significant decline in the allograft function was seen in the high-BMI-pre-sensitized group. In addition, adjusted allograft DCGI showed the poorest outcome in this group, and high BMI and HLA pre-sensitivity showed significant interaction. These could be due to several reasons. First, the nephron mass of the donated kidney might be relatively inadequate for the high BMI recipients. Simply put, it is possible that a physiologic mismatch between the recipient's metabolic demand and the donated kidney's nephron mass has an adverse allograft outcome [26]. Brenner et al. have previously proposed a nephron underdosing theory for chronic allograft failure. They suggested that the transplantation of kidneys with a relatively large nephron mass compared to the recipients' metabolic demand might lead to tolerance for future immunologic challenges, ischemic events, and CNI toxicities [27]. Hence, in high BMI recipients with high metabolic demand, kidneys with relatively small nephron mass might be more susceptible to immunologic damage when accompanied by HLA pre-sensitivity with immunologic risk, resulting in poor allograft outcomes.

Second, obesity is known to induce alloimmune dysregulation by decreasing the adiponectin level and increasing the leptin level. Adiponectin is known to inhibit B-cell lymphopoiesis, macrophage activation, T-cell proliferative response, and responses of helper T-cell (Th)-1 and Th-2 [28], and it has been reported that serum adiponectin levels decrease with visceral obesity [29]. In contrast, leptin is known to increase

T-cell response, thymocyte survival signal, and activities of neutrophils, macrophages, and natural killer cells [28], and it has been reported to be correlated with adipose tissue mass [30]. In addition, obesity is known to induce metabolic inflammation [31, 32], leading to atherosclerosis, vascular injury, and related comorbid conditions [33–35]. Especially in patients with high BMI-sensitized status, the presence of HLA-DSA might be an important factor in triggering the immune reaction. These might account for the high rate of late ABMR in the high BMI-sensitized group in our study.

Although BMI did not show a statistically significant impact on acute rejection, graft loss due to acute and chronic rejection was 75.0% in the high BMI-sensitized group, which was higher than that in the low BMI-sensitized group (50.0%) in the analysis of DCGL causes. In addition, in the high BMI-non-sensitized group, graft loss due to acute and chronic rejection was 50.0%, which was higher than that in the low BMI-sensitized group (28.6%). These results possibly indicate that when a rejection event occurs in a kidney with a relatively small nephron mass, the number of remaining functional nephrons might be smaller than in the kidney with a large nephron mass, leading to allograft failure.

This study has some limitations. First, this study was a single-center, retrospective study with a relatively small sample size of only 682 cases. The number of patients in the high BMI-sensitized group was only 21 and only 4 patients developed graft loss events. However, repeat analysis based on $\text{BMI} \geq 25 \text{ kg/m}^2$ showed results that are consistent with previous studies (odds ratio for overall graft loss 1.849, $P = 0.028$, Supplemental Table S1). In addition, this study is important because this is the first paper to analyze the relationship between the recipient BMI and HLA pre-sensitization status. The second limitation of the study is that it focuses on the recipients' condition before KT and did not analyze whether the patients developed obesity after KT. After KT, prednisolone and other immunosuppressive drugs are administered which can lead to weight gain. It is not possible to rule out that obesity developed after KT affects allograft outcomes.

Conclusions

High BMI and HLA sensitization before KT synergistically affect the long-term allograft outcomes in terms of the decline in allograft function and allograft survival in KT recipients. Our results suggest that active reduction and careful monitoring of BMI might be necessary to improve allograft outcomes especially in patients with high immunologic risk.

List Of Abbreviations

ABMR: antibody mediated rejection; ANOVA: analysis on variance; BKVAN: BK virus associated nephropathy; BMI: body mass index; BPAR: biopsy-proven acute rejection; cAMR: chronic antibody mediated rejection; CDC: complement dependent cytotoxicity; CGN: clinical glomerulonephritis; CI: confidence interval; CKD: Chronic kidney disease; CKD-EPI: Chronic Kindey Disease-Epidemiology Collaboration; CMV: cytomegalovirus; CNI: calcineurin inhibitor; DCGL: death censored graft loss; DM: diabetes mellitus; DSA: donor specific antibody; eGFR: estimated glomerular filtration rate; ESRD: end

stage renal disease; FCXM: flow cytometry-crossmatch; HDL: high-density lipoprotein; HLA: human leukocyte antigen; HLA-DSA: donor specific anti-human leukocyte antigen antibody; HR: hazard ratio; HTN: hypertension; IVIG: intravenous immunoglobulin; KT: kidney transplantation; KTR: kidney transplant recipient; LDL: low-density lipoprotein; MFI: mean fluorescence intensity; PJP: pneumocystis jiroveci pneumonia; PRA: panel reactive antibody; TCMR: T-cell mediated rejection; Th: helper T-cell; TPE: total plasma exchange; XM: crossmatch

Declarations

Ethics approval and consent to participate

This study followed the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul St. Mary's Hospital (XC15RIMI0072K).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

YP and BHC developed the study ideas; HL, EJK, and SL contributed to data collection; THB, JWM, HEY and EJO contributed to literature review and data interpretation; CWY contributed to data validation and analysis; YP contributed to generation of tables and figures; YP and BHC analyzed the data and wrote the manuscript, and all authors have read and approved the final manuscript.

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Figures

Figure 1

Distribution of the patient population according to BMI and HLA pre-sensitization status Of the 682 KTRs of ABO compatible living donor KT, 621 cases were HLA-non-presensitized, while 61 cases were HLA-presensitized. Patients were categorized into 4 groups according to the median BMI: low BMI-non-sensitized (n = 302), high BMI-non-sensitized (n=319), low BMI-sensitized (n = 40), and high BMI-sensitized groups (n = 21). Abbreviations: KTR, kidney transplant recipient; KT, kidney transplantation; BMI, body mass index; HLA-DNA, donor specific anti-human leukocyte antigen antibody; MFI, mean fluorescence intensity

Figure 2

Estimated glomerular filtration rate (CKD-EPI) during the follow-up period in the 4 groups according to BMI and HLA pre-sensitization status. Note that the decrease in allograft function tended to be higher in the high BMI-sensitized group. Abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; BMI, body mass index

Figure 3

Cumulative graft survival rate curve among the 4 groups according to BMI and HLA pre-sensitization status for death censored graft loss. Cumulative graft survival rates were significantly lower in high BMI-sensitized and low BMI-sensitized groups compared to that in the low BMI-non-sensitized group (vs. low BMI-non-sensitized; high BMI-non-sensitized, HR 1.495, $P = 0.267$; low BMI-sensitized, HR 3.377, $P = 0.036$; high BMI-sensitized, HR 4.648, $P = 0.022$). Abbreviations: BMI, body mass index; HR, hazard ratio

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