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The Effect of Body Mass Index on Graft Function and Kidney Transplant Outcomes

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THE EFFECT OF BODY MASS INDEX ON GRAFT FUNCTION AND KIDNEY TRANSPLANT OUTCOMES

By

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DEDICATION

I would like to dedicate my work to my grandparents, Gerald and Phyllis Greene and Nelson and Marilyn Galle. You have taught me the value of what hard work and education can provide through your financial and loving support of my education.

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I would like to thank my parents, Russ and Pam, and my fiancé, Chris whose never-failing support have helped encourage me to work towards my goals and to never stop until they are accomplished. Thank you for all your love, support, and encouragement.

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ABSTRACT

Background: When determining eligibility for kidney transplantation, body mass index (BMI) is often a debatable criterion for transplant due to the clinical indication, an elevated BMI has adverse effects on kidney transplant outcomes. There is a current gap in research on the effect BMI has on kidney transplant outcomes.

Purpose: The purpose of this study was to determine the role BMI plays in post-kidney transplant clinical outcomes including delayed graft function, new onset diabetes after transplant, wound complications, hospital length of stay, albumin, and readmissions to the hospital from initial hospitalization and at six months following kidney transplantation. The primary outcome of this study was to examine the relationship between BMI and delayed graft function. We hypothesize patients with a BMI less than 35 kg/m^2 is associated with fewer clinical outcomes during their initial hospitalization up to six months post-kidney transplant.

Methods: A retrospective chart review was conducted using a database including 99 patients who have had a kidney transplant and are legal adults aged 19 years or older. Data was collected at initial hospitalization and at six months post kidney transplant. Data was assessed via independent t-test, chi-square, and Mann-Whitney U test.

Results: There was no association between BMI and delayed graft function. However, there was a positive trend between increased BMI and new onset diabetes after transplant. There was also no association between wound complication and increased BMI from the time of transplant up to six months post-kidney transplant.

Conclusion: This study found an elevated BMI is not associated with an increased number of adverse clinical outcomes, but there is a positive trend between increased BMI and new onset diabetes after transplant.

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

BMI	body mass index
BUN	blood urea nitrogen
CKD	chronic kidney disease
CVD	cardiovascular disease
DGF	delayed graft function
GFR	glomerular filtration rate
GSH	glutathione S-transferase
pGSN	plasma gelsolin
UNOS	United Network for Organ Sharing
WHO	World Health Organization

INTRODUCTION

The waiting list for kidney transplantation continues to increase yearly in the United States with a median waitlist time of 3.6 years.[1] With more people in need of a kidney transplant and limited availability of kidney donors, it is necessary for donated kidneys to go to people who are in the most need and will likely have positive outcomes.[2] For that reason, patients undergo interdisciplinary team evaluations to determine a transplant recipient's social support, financial ability, psychological stability, nutritional status, and general health standing to decide if they are eligible for a kidney transplant. Patients also apply to multiple transplant centers to increase their chance for kidney transplantation. Common complications associated with kidney transplants include delayed graft function, infection, new onset diabetes, and cardiovascular events.[3] There is a current controversy in the literature regarding kidney transplantation complications specifically surrounding the role overweight and obesity play in post- kidney transplant complications.

Obesity, as defined by the World Health Organization (WHO) is a body mass index (BMI) > 30 kg/m^2. Over the past years, obesity has been on the rise within the United States population to the point of one in three Americans are now considered obese.[4] With an increase in the nation's obese population, more obese patients are receiving transplants than ever before. Of people with end stage renal disease, one in two individuals are obese.[4] In previous studies, it has been noted obese patients have poorer outcomes post-kidney transplantation compared to non-obese patients. Additional studies have found no association between obesity and post-transplant outcomes. It remains unclear how BMI prior to transplant can affect the overall kidney transplant outcomes.

The role BMI plays in kidney transplant outcomes is important because it is a factor used in patient evaluation for kidney transplantation. People who are denied kidney transplant waitlist status due to obesity, are encouraged to pursue weight loss, and even bariatric surgery prior to

becoming active on the kidney transplant waitlist based off their BMI measurement. Currently, BMI is the most common reason for initial inactive status on the kidney transplant waitlist.[3] With research in this area being contradictory, there are currently no national BMI standards of practice for kidney transplantation. The final decision is ultimately left up to the transplanting facility to choose who is eligible for a kidney transplant. The purpose of this study is to determine the effect BMI has on graft function in the initial months following kidney transplant. This study also seeks to identify other effects BMI has on post-kidney transplant outcomes including, wound complications, hospital length of stay, new onset diabetes mellitus, and readmissions to the hospital following transplantation up to six months post-kidney transplant. We hypothesize a BMI less than 35 kg/m^2 is associated with fewer clinical outcomes during their initial hospitalization and up to six months post-kidney transplant. From the study analysis and results, evidenced-based decisions will be used to determine the role BMI should play in the kidney transplant evaluation process.

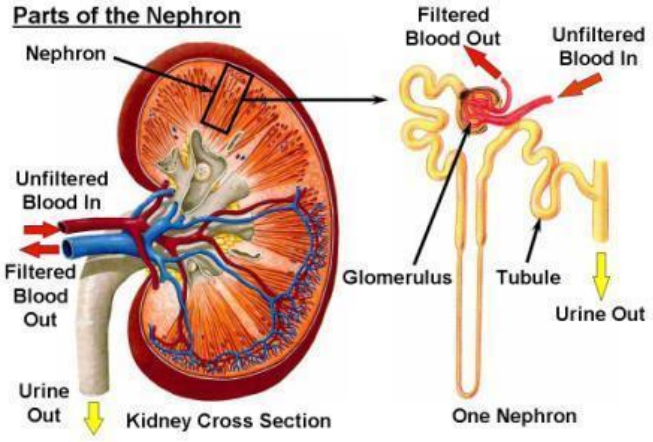
REVIEW OF LITERATURE

Obesity

Obesity is classified by the WHO based on BMI. A BMI less than 18.5 kg/m^2 is classified as underweight, 18.5-24.9 kg/m^2 is normal weight, 25.0-29.9 kg/m^2 is overweight, 30-34.9 kg/m^2 is class 1 obesity, 35-39.9kg/m^2 is class 2 obesity and greater than 40 kg/m^2 is class 3 obesity. Obesity has been constantly rising in the United States population for many years.[5] This rise in obesity has been reflected in the kidney transplant waiting list and evaluation patients. Of the patients with end stage renal disease, one in two patients are obese.[4] The role BMI plays prior to kidney transplant remains unclear on the effect on post-kidney transplant outcomes.

Chronic Kidney Disease

The main function of the kidneys is to maintain homeostasis of the fluid and electrolytes balance in the blood. This is done through the removal of waste and excess water from the blood through the production of urine to excrete the waste from the body along with mineral regulation. This process occurs after the blood is delivered to the kidney's glomeruli through the capillaries in the kidney. The filtered blood collects in Bowman's capsule, which contains the glomerulus, and then goes through the tubules lined with filtrating cells to reabsorb water and minerals of use for the body. The waste is then secreted in the form of urine and exits the kidney through the ureter to the bladder and is excreted from the body via the urethra. The kidneys also produce hormones including, calcitriol (the active form of



vitamin D), erythropoietin, and renin. Calcitriol regulates the absorption of calcium and phosphorous promoting bone strength. Erythropoietin stimulates the bone marrow to produce red blood cells, and renin regulates blood volume and pressure.[6] All of these functions are affected in chronic kidney disease (CKD).

CKD is a progressive scarring on structures of the kidney due to various conditions such as diabetes, hypertension, infection, polycystic kidney disease, kidney malformations, glomerulonephritis, and more. It usually occurs gradually and the disease is divided into 5 stages. Stage 1 is the least severe form of CKD and the disease can progress to stage 5 leading to end stage renal disease when there is little to no kidney function. In the early stages of CKD, people tend to have minimal or no symptoms at all. As kidney function decline becomes more significant, CKD becomes more apparent. The loss of kidney function impairs the ability to maintain homeostasis and ability to produce urine which leads to an accumulation of water causing edema, excess waste, and an increase in toxic substances in the body. The treatment for CKD aims to slow the progression of kidney damage by controlling the underlying cause. When CKD progresses to end stage renal disease then the damage has been done to the kidney and the only option for these patients is dialysis, a mechanical filtration of the blood, or a kidney transplant.[7]

Delayed Graft Function

A transplanted kidney is also called the graft and it is expected to begin working immediately following transplantation. Delayed graft function (DGF) is characterized by acute rejection, oliguria, elevated blood urea nitrogen (BUN), elevated creatinine, low glomerular filtration rate (GFR), and the need for dialysis within one week post kidney transplant. Some risk factors for DGF include longer operating time and longer cold and warm ischemic time.[8, 9, 10] Cold ischemic time is the amount of time between the chilling of the organ after its blood supply

has been cut off to the time the blood supply is restored and the organ is warmed. Warm ischemic time is the amount of time an organ remains at body temperature after its blood supply has been stopped or reduced. DGF is treated with dialysis and/or diuretics[11] to aid the performance of the graft in the hopes it will begin to function. DGF is associated with poor 1-year graft survival.[12] However, this is difficult to determine due to immunosuppression nephrotoxicity and other factors which play a role in inhibiting long-term graft survival. For the purpose of this study, DGF will be assessed initially post-transplant and will not be reassessed at six months post-transplant.[14, 15] A review article examined the different ways to determine and manage DGF. Out of the 30 studies reviewed between the years of 1984-2007, 69% of the studies determined DGF by the use of dialysis within the first seven days post-transplant as the most accurate assessment tool of DGF.[12, 13]

Currently, some literature found obesity has an effect on the occurrence of DGF while other studies have found no association between obesity and DGF. Chan et al completed a meta-analysis to review relevant literature assessing the role of pre- and post-transplant obesity on patient graft survival. It was concluded literature in this area is very controversial when determining the effect of obesity on graft function following kidney transplantation.[16] A retrospective study by Pham P et al completed a similar meta-analysis, but it analyzed different studies than Chan et al. The aim of this study was to determine the impact of obesity on transplant candidates and aid in the decision of whether or not to transplant these patients. Graft function was analyzed in twenty different studies with multiple studies reviewing the UNOS database at different time points. A similar conclusion was met, this is an area of discrepancy and more research is still needed.[17]

Many studies have found obese patients have an increased incidence of kidney rejection or decreased graft survival compared to non-obese patients. One specific study by Grosso et al investigated the association between BMI and graft survival evaluating BMI as both a continuous

and categorical variable. They found BMI is an independent risk factor for graft loss in the study even following adjustment for obesity related risk factors including diabetes, cardiovascular disease, smoking, and hypercholesteremia. It showed 42.9% of obese patients had DGF whereas 7.7% of normal weight patients had DGF with a p-value of 0.035.[18] Another study evaluated 2,161 kidney transplant patients and found obesity prior to kidney transplant had a 36.8% increase in risk of graft failure 95% CI, 2.174-941.422 and a p-value <0.001.[19] While another study with 19,882 subjects found BMI is an independent risk factor for DGF with OR 1.34 and p<0.001 for overweight subjects and OR 1.65 with p<0.001 for obese and OR 1.92, p<0.001 for morbidly obese subjects.[20]

Although some studies have found an association between BMI and DGF, multiple studies have found no association between obesity and DGF. Karabicak et al looked at a predominately African American population, which is a population at increased risk of obesity and found no significance between obesity and graft function following kidney transplantation with a p-value >0.005.[21] Another study reviewed 3,054 patient records from 1998-2008 to evaluate patient and graft survival along with transplant complications based off of patient's BMI. They found all transplant recipients had similar graft survival regardless of BMI.[22] Zrim et al evaluated 550 patients and found weight was not significantly associated with graft failure with a mean of 1.019 and 95% confidence interval 0.996-1.042 and p-value of 0.1.[23] A study at the University of Michigan had 869 subjects to gain an understanding on whether obesity had other risks beyond developing surgical site infection in kidney transplant recipients. They found obesity had no independent effect on graft function.[23] Moreira et al completed a study in Brazil with 471 kidney transplant recipient and determined there is no association between BMI and graft function with a p-value <0.05.[24]

Multiple studies did not find an association but detected a trend in the data collected towards obesity not being a contraindication for kidney transplantation. Kiexszek et al reviewed

859 patient charts and found BMI did not influence the effect of DGF, but there was a positive trend in the data for obese patients and DGF. Patients with a higher BMI at transplant had an increased incidence of graft failure.[14] A large cohort study with 11,836 kidney transplant recipients found increased BMI is a risk for DGF after extensive multivariate adjustment,[9] but the data was not significant enough to have an association between the two variables. These results indicate there is a variety of research in this area, but the research is quite contradictory indicating a need for more research.

Wound Complications

Following kidney transplantation, patients are placed on immunosuppressive and corticosteroid medications to prevent organ rejection. These medications must be balanced between immunosuppression and infection risk along with individualization for the patient's particular needs.[25] Due to the use of immunosuppressive medications and other factors, infection is the leading cause of mortality during the first year following kidney transplant.[26] If an infection progresses it affects graft function and thus patient survival. Since infections are also known to be a complication of surgery in obese patients, the question arises, are certain populations at increased risk for infection post-transplant?

The literature in this area still needs more research as many studies have not found a common BMI in relation to infection incidence. One study reviewed 642 kidney transplants from 1999-2007 and found obese patients with BMI greater than 30 kg/m^2 had an increase incidence of deep wound infections related to mechanical factors such as cleaning the wound due to delayed healing with a p-value of 0.001.[27] However, another study associated a BMI greater than 35 kg/m^2 with a higher incidence of wound dehiscence and those patients had ten times more infectious events per year than those with a BMI less than 35 kg/m^2.[22] Two other studies assessed BMI as a predictor of early infection and bacteremia in the post-transplant period and both found

an association between BMI, early infection and bacteremia with a p-value of <0.001. This indicated a high BMI is a predictor of infection in post kidney transplant patients [25, 26, 28] These studies simply associated an increase in infection with an increase in BMI, but they did not associate a particular BMI point at which the increase infection occurred.

New Onset Diabetes After Transplant

Diabetic nephropathy is a leading cause of kidney disease. It is characterized by the thickening of the glomerular basement membrane which progresses to glomerulosclerosis. New onset diabetes after transplant occurs for a variety of reasons, one of which is due to immunosuppressive medications producing a toxic effect on insulin production and an increased resistance to insulin.[29] It is reported there is a 20.5% incidence of new onset diabetes after transplant which is associated with increased mortality and increased rates of cardiovascular disease and infection.[30] Risk factors for the development of new onset diabetes after transplant consist of being greater than 45 years of age, family history of diabetes, African American or Hispanic race/ethnicity, use of corticosteroids, HIV, hypertension, and proteinuria.[31] To determine the occurrence of new onset diabetes after transplant the use of hypoglycemic agents for any blood glucose greater than 200 mg/dL or fasting blood glucose greater than 140 mg/dL is used for evaluation along with leaving the hospital with hypoglycemic agents.[31] Following transplantation, blood glucose will spike even if they were normal prior to transplant.[12]

Many studies have found an association between obesity and new onset diabetes after transplant. Between May 2000 and December 2005, 250 Caucasian patient's blood glucose levels were followed up to 32 months. An association was shown between patients with a BMI of 28.1+/-3.4 kg/m^2 with a p-value of 0.002.[32] Another study associated patients with a higher BMI at an increased risk of hyperglycemic events.[33] Other studies have found a BMI greater than 30

kg/m^2 had a higher incidence in new onset diabetes after transplant with a p-value <0.001.[22, 24] There is still some discrepancy as other studies have failed to demonstrate an association between obesity and the development of new onset diabetes after transplant. Other studies question if the association is dependent of body fat distribution more than BMI.[34] Another study demonstrated an elevated pre-transplant glucose as a risk factor for new onset diabetes, however, this was also difficult to determine due to the timing of transplant surgeries. Since many patients are called in at a moment's notice, researchers were unable to control for patients most recent meals in relation to pre-surgery blood glucose lab collections.[33] Although new onset diabetes is a common complication after kidney transplant it is uncertain the best way to predict who is at risk and the role BMI plays in the development of new onset diabetes.

Obesity and Chronic Kidney Disease Mechanism

Obesity affects individuals in every stage of CKD and can play a role in the progression of kidney disease.[35] For people with CKD, as BMI increases multiple reports believe obese patients develop sarcopenic obesity. Sarcopenic obesity occurs when a person has excess weight. This form of obesity is classified by a loss in muscle mass and an increase in fat mass. It occurs primarily in people who are elderly, inactive, have inflammation or have a chronic disease.[36] With a decrease in muscle mass, gelsolin, an actin-binding protein produced by the skeletal muscle, will also decrease. There are two forms of Gelsolin, pGSN which is actively secreted into the extracellular space and cytoplasmic GSH which participates in the intracellular space. In the obese, pGSN is depleted by inflammatory mediators leading to a decreased production of protein due to decreased skeletal mass. Depletion of pGSN increases with the degree of systemic inflammation and muscle wasting. In dialysis patients, increased levels of Gelsolin has been associated with increased survival and it has begun to be used as a therapeutic marker in CKD patients awaiting a kidney transplant.[37]

As muscle mass decreases, gelsolin, along with skeletal, respiratory and cardiac muscle function also decrease. This leads to impaired muscle-based oxidative mechanisms and a decrease in oxidative defense. Sarcopenic obesity also increases fat mass and visceral adiposity leading to decreased inflammatory markers including adiponectin, visfatin, resistin, interleukin-6, high sensitivity C-reactive protein, prothrombin fragments 1+2, thrombomodulin, and vascular cell adhesion molecules. All together cellular inflammation increases.[16] The inflammation contributes to focal and segmental glomerulonecrosis and glomerulosclerosis.[19] In return, cardiovascular disease risk increases, while patient survival and graft survival decrease.

Surgical Complications of Obesity

Obese patients have an increased risk of postoperative complications and obesity is an independent risk factor for surgery. [27, 38, 39] Surgical literature has well established the risk of wound and surgical site infections in obese patients.[40] More specifically, obesity is positively associated with increased difficulty when operating, increased operating time, delayed wound healing, cardiovascular disease and increased wound complications including wound dehiscence and breakdown.[23, 39] Due to these complications many insurance companies began to deny coverage for candidates with a BMI greater than 40 kg/m^2 for kidney transplantation[1, 27] providing another obstacle for transplantation.

METHODS

Study Design and Participants

This was a retrospective, electronic medical record review on all patients who received kidney transplants from November 6th, 2013 – October 4th, 2014. The study protocol was approved by the Institutional Review Board at University Nebraska Medical Center in Omaha, Nebraska. Patients were excluded if they were less than 19 years of age or if they had multiple organ transplants at the time of kidney transplantation. No patients were excluded from this study based on clinical acuity. After extensive chart review, 99 kidney transplant recipients were eligible for this study.

Data Collection

All data was collected at three time points; this includes initial hospitalization admission, discharge, and at six months post-kidney transplant. Data on readmissions to the hospital or emergency room documented in the medical record from initial hospitalization up to six months post kidney transplant and a chart audit was performed to assess the accuracy of data collection at three months. The following information was collected at the initial hospitalization for kidney transplant admission: body mass index, height, weight, past medical history including the cause of kidney disease, history of cardiovascular disease, hypertension, hyperlipidemia, diabetes, and if the patient was on dialysis prior to kidney transplantation. Albumin was a laboratory value collected at admission to the hospital as this is a pre-transplant indicator for disease status. Demographic information was also collected for all participants including, age, gender, race and ethnicity.

At discharge from initial hospitalization for a kidney transplant, data for the primary outcome of this study, DGF, defined as the use of dialysis within the first week after

transplantation was documented. Wound complications were recorded and followed up to six months post-transplant. Wound complications were documented in the event of a wound nurse consult, the use of a wound vac, wound opening, or wound infection. To determine transplant related diabetes, hyperglycemic events with blood glucose >200 mg/dL were recorded along with the prescription of insulin or oral hypoglycemic agents at discharge. Throughout the initial hospitalization, the length of stay was calculated as the number of days post kidney transplant operation.

The electronic medical record was reviewed at six months post-kidney transplant follow-up appointments with the nephrologist. Previous appointments were reviewed to ensure no information was missed and data recorded was accurate. The following information was collected at the six month time periods: new wound infection or wound drain, a new use of insulin or oral hypoglycemic agents, and BMI was documented. Readmission and the reason for readmission in the past six month's post-kidney transplant were also documented. All information was documented by the incidence occurrence. If a patient had a wound vac once at three months and still had the wound vac at six months this was only documented as one event. This data was all compiled on an excel spreadsheet and patient identifiers were not recorded. All collected information was reviewed for accuracy and corrected if an electronic error occurred. All available information on each patient was included in the analysis and is displayed in the tables.

Data Analysis

BMI data was categorized into two groups, BMI <30 kg/m^2 and BMI >30 kg/m^2 to be compared. Although our original hypothesis was predicted for a BMI greater than 35 kg/m^2, due to the distribution of the data a dichotomous decision was made to change the BMI groupings

based on the data to BMI > 30 kg/m^2, which is also the WHO classification for obesity. The differences between categorical variables were evaluated with the chi-square test. Categorical variables including gender, race, ethnicity, history of CVD, hypertension, hyperlipidemia, diabetes, and prior use of dialysis, DGF, new onset diabetes after transplant, wound complications, diabetes diagnosis six months post-transplant, and readmission to the hospital were used for chi-square test analysis. The significance was determined by Pearson chi-square. To analyze continuous variables, an independent t test was used. The continuous variables include the length of stay and albumin. A Mann-Whitney U test was then used to compare the distribution between groups to ensure statistical significance for variables that may have been affected by outliers. Data analysis was performed using IBM SPSS Statistics 23 software and p-values of < 0.05 were considered significant.

RESULTS

Among the 99 patients included in the study, the mean age was 52.9 years old and 53% of the patients had a BMI > 30 kg/m^2 classifying them as obese. The majority of patients were Caucasian consisting of 78% of the patient population and 61.6% of the patients studied were males. In this study, there were no underweight patients and all the patients fell between a BMI of 20.34 kg/m^2 and 62.3 kg/m^2. Baseline characteristics collected upon admission to the hospital are displayed on Table 1 and there was no significant difference between group 1, BMI < 30 kg/m^2 and group 2, BMI > 30 kg/m^2 at admission to the initial hospitalization for kidney transplantation.

The most common cause of a patient's CKD leading to the need for kidney transplantation was diabetic nephropathy (22%) and hypertension (20%). Lesser common causes include polycystic kidney disease (12%) and glomerulonephritis (4%). Groups were determined based off the distribution of data. Group 1 was chosen for patients with a BMI < 30 kg/m^2 and Group 2 contains patients with a BMI > 30 kg/m^2. The difference between groups at discharge from initial hospitalization for kidney transplantation outcomes are found on Table 2. A lower BMI had a slightly increased albumin by 0.014mg/dL. This increase is very minimal and was not statistically significant.

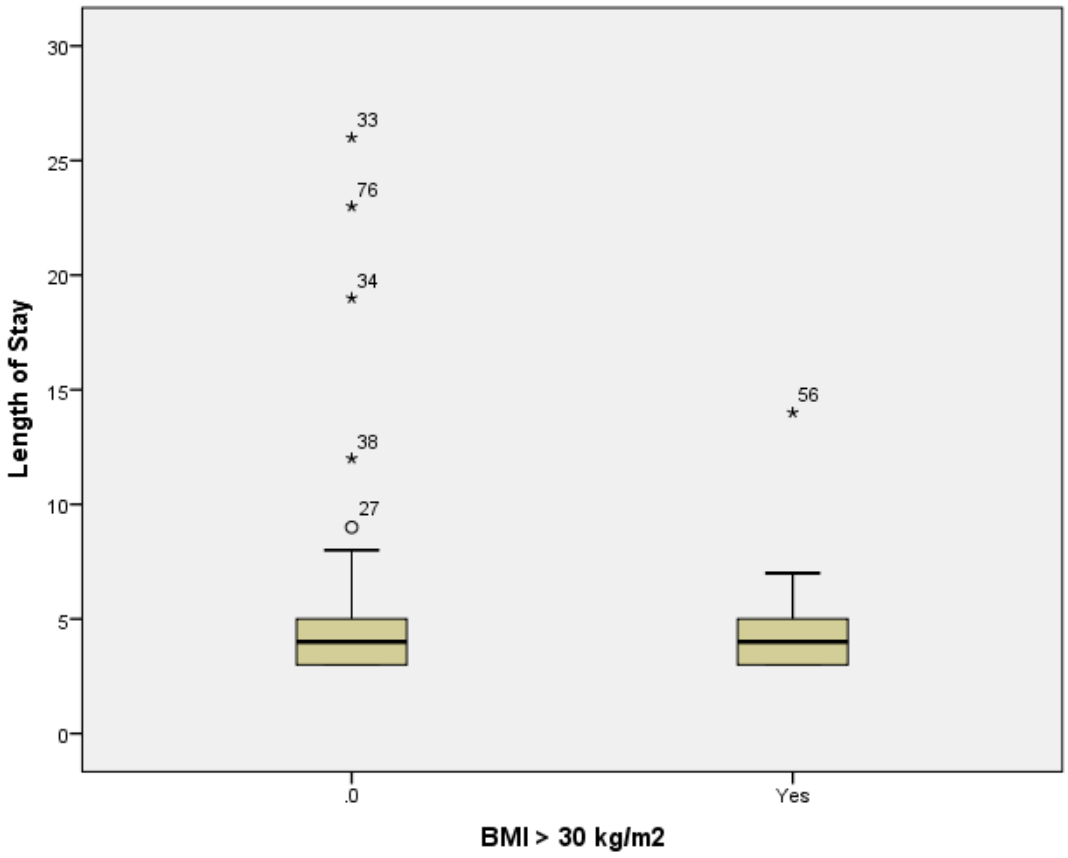
Initial Hospitalization

Table 1: Baseline Characteristics				
Variable	Total	BMI <30 kg/m^2	BMI >30 kg/m^2	p-value
Total	N=99	47	52	
Mean BMI		26.5	34.9	0.053
Gender-M/F	61/38	26/21	35/17	0.221
Mean Age (years)	52.9	50.8	54.8	
Ethnicity (Hispanic/Non-Hispanic)	8/91	44/3	47/5	0.556
Race				0.720
Caucasian	76	38	38	
African American	15	5	10	
Hispanic	3	2	1	
American Indian	2	1	1	
Other	3	1	2	
History of CVD	17	9	8	0.620
History of Hypertension	84	37	47	0.106
History of Hyperlipidemia	43	22	21	0.520
History of Diabetes	34	13	21	0.183
Prior Use of Dialysis	75	37	39	0.789
Albumin (mg/dL)	99	3.606	3.592	0.837

Discharge from Initial Hospitalization

Table 2: Initial Hospitalization Outcomes			
	BMI < 30 kg/m^2	BMI > 30 kg/m^2	p-value
Delayed Graft Function	8.1 % (8/99)	10.1% (10/99)	0.810
New Onset Diabetes After Transplant	13.1% (13/99)	14.1% (14/99)	0.070
Length of Stay (days)	5.6	4.5	*0.003*

Figure 2: Length of Stay Distribution

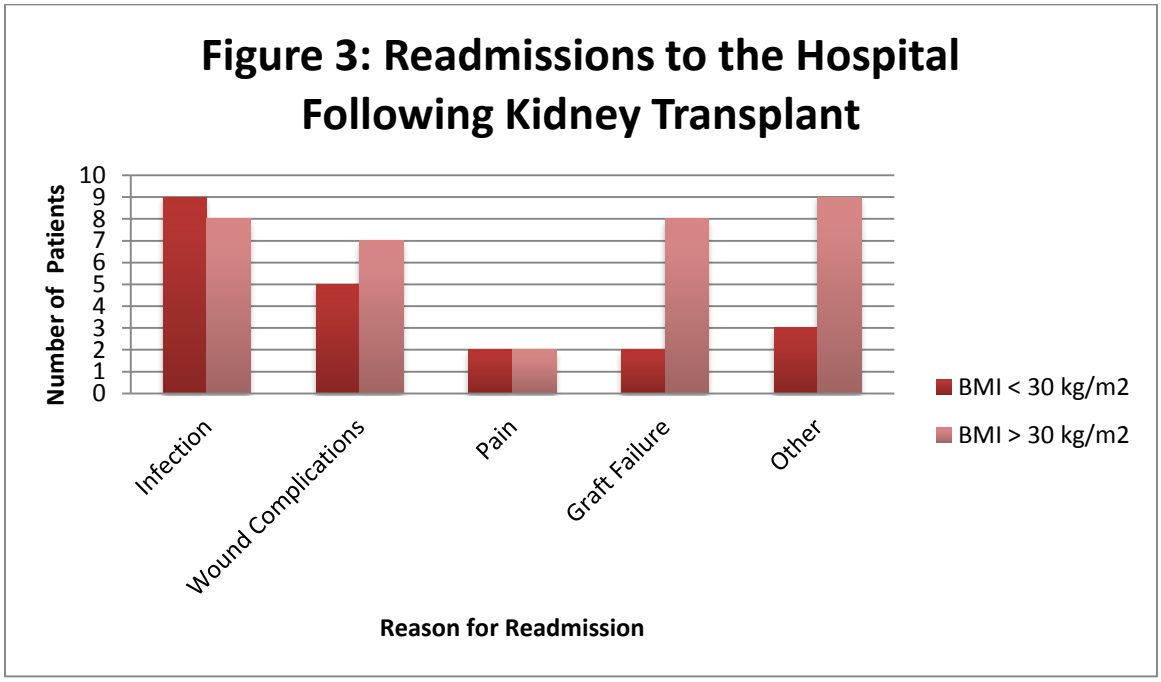


A chi-squared test was performed and no relationship was found between DGF and BMI. A positive trend was found between patients with a BMI > 30 kg/m^2 and new onset diabetes after transplant (p=0.07, Table 2). The independent t-test revealed a significant relationship between the two groups for hospital length of stay. This indicates a lower BMI is associated with a longer length of stay than a BMI > 30 kg/m^2. Due to concerns about outliers as seen in Figure 2 making this a false significant finding, a Mann-Whitney U test was conducted to compare the distributions between groups and the length of stay using the median had a p-value of 0.805. This test indicates the difference in the distribution for length of stay was not significant.

Following hospitalization for a kidney transplant, patients were reassessed at six months. No association was found between groups for wound complications, new diabetes diagnosis, or readmissions to the hospital as seen on Table 3. The most common reasons for readmission to the hospital were infection, pain, graft failure, or wound complications depicted on Figure 3.

Six Months Post-Kidney Transplantation

Table 3: Outcomes Post- Initial Hospitalization			
	BMI < 30 kg/m^2	BMI > 30 kg/m^2	p-value
Wound Complications	9.1 % (9/99)	10.1% (10/99)	0.992
DM Diagnosis	14.1% (14/99)	19.2% (19/99)	0.506
Readmission to Hospital	23.2% (23/99)	32.3% (32/99)	0.595



Based on our original hypothesis, we expected to find patients with a BMI less than 35 kg/m2 are associated with fewer clinical outcomes during their initial hospitalization and up to six months post-kidney transplant. Once the data was collected, based off the distribution of the data patients were placed into different groups. However, statistics were completed to compare the data between Group 1 with BMI <35 kg/m^2 and Group 2 with a BMI >35 kg/m^2. In light of the hypothesis, Table 4 provides baseline characteristics for these new groups. Due to the distribution of the data there was a statistically significant difference in race and history of diabetes between groups.

Initial Hospitalization

Table 4: Baseline Characteristics for BMI > 35 kg/m2

Variables	Total	BMI < 35 kg/m^2	BMI >35 kg/m^2	p-value
Total	N=99	81	18	
Gender-M/F	61/38	49/32	12/6	0.626
Mean Age (years)	52.9			
Ethnicity (Hispanic/Non-Hispanic)	8/91	8/73	0/18	0.164
Race				*0.031*
Caucasian	76	65	11	
African American	15	8	7	
Hispanic	3	3	0	
American Indian	2	2	0	
Other	3	3	0	
History of CVD	17	14	4	0.530
History of Hypertension	84	68	16	0.597
History of Hyperlipidemia	43	35	8	0.924
History of Diabetes	34	24	10	*0.036*
Prior Use of Dialysis	75	59	16	0.072
Albumin	99	3.636	3.433	0.264

A chi-squared test was performed on DGF and new onset diabetes after transplant. There appeared to be associations with BMI less than 35 kg/m2 and DGF, but due to the distribution of the data the tests were not valid as seen on Table 5. There was no significance between groups for new onset diabetes after transplant. A trend was found between a BMI > 35 kg/m^2 and fewer readmissions to the hospital with a p-value of 0.007 as seen in table six. The distribution of the data likely impacted the trend in readmissions. The independent t-test revealed no significant relationship between the two groups for hospital length of stay.

Discharge from Initial Hospitalization

Table 5: Initial Hospitalization Outcomes for BMI >35kg/m^2

	BMI < 35 kg/m^2	BMI > 35 kg/m^2	p-value
Delayed Graft Function	15.2 % (15/99)	3% (3/99)	0.034*
New Onset Diabetes After Transplant	21% (21/99)	6% (6/99)	0.471*
Length of Stay	5.06	4.72	0.674
Creatinine			

*1 cells (25%) have expected count less than 5. The minimum expected count is 3.27 and 4.91 respectively. These tests are not valid.

Six Months Post-Kidney Transplantation

Table 6: Outcomes Six Months Post Kidney Transplant for BMI >35kg/m^2

	BMI < 35 kg/m^2	BMI > 35 kg/m^2	p-value
Wound Complications	17.2 % (17/99)	3% (3/99)	0.090*
DM Diagnosis	22% (22/99)	11.1% (11/99)	0.306
Readmission to Hospital	47.5% (47/99)	8.1% (8/99)	*0.007*

*1 cells (25%) have expected count less than 5. The minimum expected count is 3.45. These tests are not valid.

DISCUSSION

The present study evaluated BMI and its effect on DGF along with other kidney transplant outcomes including new onset diabetes after transplant, wound complications, length of stay, and mean albumin on admission for transplant. Many reports have noticed a trend in patients with a higher BMI having worse outcomes following kidney transplantation. Multiple studies have been completed, but the results in this area have been contradictory.[16] As a result, there are no national guidelines for limiting waitlist candidacy based off of BMI and transplant centers have had difficulty determining whether a BMI limit should be set for their own facility. This study found no association between BMI and DGF; however, a trend is prevalent between increased BMI and the occurrence of new onset diabetes after transplant.

Delayed Graft Function

The primary aim of this study was to determine the effect of BMI on DGF. Although no association was found between BMI and DGF, patients in the second group, BMI greater than 30 kg/m^2 had a 2% increase in DGF occurrence. Of the patients with DGF, 3% had a BMI greater than 35 kg/m^2. This result was not significant, but the results may have been affected by our inability to assess graft failure in patients who were not previously on dialysis since the indicator was to have dialysis within seven days post-transplant. Roughly one fourth of the patients surveyed were unable to be assessed for DGF via the use of dialysis. Although it is possible for dialysis to be used, these patients typically begin a diuretic regimen[12, 13] which was not captured during the medical record review. Of patients involved in the study, 27% had no previous use of dialysis and we were likely unable to assess DGF based off the use of dialysis. When comparing groups of patients on dialysis prior to transplant there were 37 in group 1 and 39 in group 2 with a

p-value of 0.789 indicating this difference was not statistically significant and should have limited effect on our results.

New Onset Diabetes After Transplant

Due to the use of immunosuppressive agents, corticosteroids and other factors after kidney transplantation new onset diabetes is prevalent in these patients.[29] A trend was found between a BMI greater than 30 kg/m^2 and an increased occurrence of new onset diabetes after transplant. When comparing diabetes diagnosis between initial hospitalization and at six months post-transplant, the majority of patients with a BMI less than 30 kg/m^2 were diagnosed with diabetes by discharge from the hospital and only 1% were diagnosed at six months post-transplant. In group 2, a majority of patients were diagnosed after initial hospitalization with a 5% increase in diagnosed by six months post-kidney transplant.

This positive trend is likely similar to the increased occurrence of Type 2 Diabetes in obese individuals. Type 2 diabetes is three to seven times greater in those who are obese than normal weight adults. If obese patients are already at increased risk for type 2 diabetes prior to kidney transplantation then the additional factor of corticosteroid use and it is likely this trend will occur in a majority of obese kidney transplant recipients.[41] Of the 99 patients, 34 were previously diagnosed with diabetes. Of those 34 patients, 22 had the cause of their kidney disease from diabetic nephropathy. However by six months post-kidney transplant, 53% of the patients studied had a diagnosis of diabetes at some point during the study. Hypertension is another factor that has been associated with an increased occurrence of new onset diabetes after transplant.[31] In this study, 47% of patients with a BMI greater than 30 kg/m^2 had a history significant for hypertension. We question if this may have had an impact on the trend seen between BMI greater than 30 kg/m^2 and new onset diabetes after transplant.

Wound Complications

There appears to be no statistical significance between wound complications and BMI with roughly equal proportions of wound complications between groups. This result was surprising because multiple research studies associated increased BMI as a predictor for wound infection and poor wound healing. [2, 22, 26] Literature suggests wound complications are more prevalent in the obese population and the area of contention is in regards to which BMI has the most significant complications. Some studies found a BMI greater than 30 kg/m^2 to have an association with increased wound complications while other studies suggest wound complications are associated with a BMI greater than 35 kg/m^2. These results were not replicated in the present study. This study found no association between BMI at either limit of 30 kg/m^2 or 35 kg/m^2. The distribution of data between the BMI greater than 35 kg/m^2 likely impacted the results, as only 18 of the 99 patients studied had a BMI greater than 35 kg/m^2.

Another factor may be physician preference throughout the kidney transplant evaluation process. Transplant centers, in coordination with UNOS aim to provide an organ to a patient who will have positive outcomes. If a patient is at a greater risk for wound complications it is possible they are too compromised and not chosen for transplant. This is not uncommon because infection is the leading cause of one year mortality in kidney transplant patients. When comparing our results to current literature this is an indicator that could use more research.

Length of Stay

When comparing hospital length of stay between the two groups the results were opposite of what was predicted. A BMI less than 30 kg/m^2 had a longer length of stay than patients with a BMI greater than 30 kg/m^2. This was thought to be due to outliers based off the box plot in figure 2, so a Mann-Whitney U Test was completed to determine if outliers had an effect on the

significance of our results. Following completion of the Mann-Whitney U test it appears the results were still statistically significant and the distribution of the data is not significant for outliers. Literature often found an association between increased BMI and an increased hospital length of stay. In fact, during the transplant evaluation process increased length of stay is a reason given to patients who have a higher BMI when asked why there is a BMI limit for kidney transplantation at Nebraska Medicine. Based off our results this is not an adequate explanation as patients with a BMI lower than 30 kg/m^2 was associated with an increased length of stay. It is possible length of stay had an impact on our other results such as wound complications, because increased length of stay also has been associated with increased wound infections.[26] So, there may have been more wound infections in the BMI less than 30 kg/m2 group due to the longer length of stay. More research would need to be completed to determine if this is a plausible possibility.

Albumin

Although albumin is not used as a marker for nutritional status, per KDOQI guidelines it is still used for assessment and the goal is for albumin to be greater than 4.0 mg/dL for the best outcomes.[42] Albumin is specifically used as an outpatient marker because a lower albumin has been linked to increased mortality in patients on the kidney waitlist and it is one lab not affected by fluid status. When compared between the two groups there was no association found between albumin levels. There was a slight increase in albumin noticed in the BMI less than 30 kg/m^2 group, but the difference was not significant. The albumin lab value obtained is a reliable indicator as it was taken on admission to the hospital. At admission to the hospital, patients should not have an inflammatory response negatively affecting the laboratory value and assessment.

Study Population

Of the study population, a majority of the patients were Caucasian. This may have impacted this study because many of the risk factors for development of new onset diabetes were dependent on race and ethnicity. Patients of African American or Hispanic race and ethnicity are associated with an increased risk in development of new onset diabetes after transplantation.[21] This should not have had an impacted DGF based off the study completed by Krabicak et al which reviewed a predominately African American population and found no effect on DGF.[21] It is also important to note the mean BMI between groups was close to statistical difference with a p-value 0.053 indicating these two groups mean BMI was different enough we should have been able to tell a difference between the two groups. This study represents the patient population at Nebraska Medicine and likely contributes to the controversy in the literature regarding BMI and kidney transplant outcomes.

Comparative Research

The results from our study coincide and differ with other studies of similar context analyzing the effect of BMI on DGF. In comparison, our study found no association between BMI and DGF similar to a study which evaluated 550 patients and found weight was not significantly associated with graft failure with a mean of 1.019 and 95% confidence interval 0.996-1.042 and p-value of 0.1.[23] This study also examined the effect of induction therapy impacting graft survival. It remains unclear if our population would have valued from a similar intervention. The University of Michigan had 869 subjects and determined obesity had no independent effect on graft function similar to our results. Our study also found a trend between higher BMI and new onset diabetes after transplant. Similar studies have found associations between high BMI and new onset diabetes after transplant. One study collected 250 Caucasian patient's blood glucose levels and followed the patients up to 32 months. An association was

shown between patients with a BMI 28.1+/-3.4 kg/m^2 with a p-value of 0.002.[32] It is uncertain if our study would have benefited from a closer following of patients' blood glucose levels. Other studies similar to ours found a BMI greater than 30 kg/m2 had an increased incidence in new onset diabetes after transplant with a p-value <0.001.[22, 24]

In contrast, while our study did not find an association between BMI and graft failure other studies have shown an association. One specific study evaluated BMI and graft survival by evaluating BMI as both a continuous and categorical variable. This is an area for improvement in our study as it was unable to be completed due to time constraints. Another study associated BMI as an independent risk factor for graft loss in the study even following adjustment for obesity related risk factors including diabetes, cardiovascular disease, smoking, and hypercholesteremia. Our study did not adjust for risk factors and other confounders given our results it was likely they did not have a significant impact in our study, yet this is another area for improvement within our study,[18] specifically comparing new onset diabetes after transplant it would be necessary to control for race/ethnicity and hypertension as these are known risk factors. Another study evaluated 2,161 kidney transplant patients and found obesity prior to kidney transplant had a 36.8% increase in risk of graft failure 95% CI, 2.174-941.422 and a p-value <0.001.[19] While other studies found no association between BMI and new onset diabetes after transplant however this research is less contradictory than BMI and DGF as a majority of research has found an association or a trend similar to our study.

A majority of these studies had a much larger sample size than our study and contradictory research still exists so it is uncertain the effect our sample size played in our results. Although there is a variety of research in this area, the results remain contradictory between BMI, graft failure, and other transplant related outcomes. It is important to note the sample sizes in a majority of these studies are very larger and data was collected from multiple hospitals over an extended period of time. This likely played a role in the studies lack of associations as they

difficult to control for the variable factors between facilities and kidney transplant approaches at the hospitals may have changed over the course of time. It is imperative for the health professionals to know the research and to be aware of the risks involved with kidney transplantation.

Limitations

This is a retrospective chart review; bias may have arisen owing to misclassification errors. Sample size may also be a potential source of bias as a larger sample size may have strengthened associations. Another limitation includes the inability to assess DGF in patients who did not have dialysis access. Of those patients studied, 73% of the patients had dialysis access. Since we collected data based off of use of dialysis within seven days after transplant it is likely some patients may not have been captured since 27% of patients had not had previous dialysis and may not have had dialysis to treat their DGF following transplant.

Another limitation may be patients fluid status at time of admit and BMI documentation. Patients with end stage renal disease have fluctuating fluid status and it is possible they were fluid overloaded at admission falsely elevating their BMI. Since transplantation is unknown many of these patients may or may not have had dialysis prior to transplant hospitalization. However, if patients were compromised by the amount of fluid on them then they are either not transplanted or sent to dialysis prior to transplant, even so BMI may have been falsely elevated for evaluation as it is documented on admission.

Using BMI to evaluate nutritional status is another limitation as BMI is a poor predictor of lean body mass or body fat so BMI is a limited marker, however since it was a retrospective study this was the only marker available for use given its limitations. Due to time constraints more detailed statistics were unable to be completed; however it is an area for improvement and

advancement in this study. The sample size is also a limitation of this study especially when comparing the sample size to the sample size in the studies reviewed in the literature review section.

Strengths

A strength of this study is the BMI distribution. There was a variety of BMI values and an equal distribution of the data. This allowed for all BMI's to be captured in the analysis of the data. The patient population was very representable of the population treated at Nebraska Medicine and allows the results of this study to be applied to clinical practice.

Applications for Clinical Practice

Interest in this study developed from the varying BMI limitations set at Nebraska Medicine's kidney transplant center. Throughout the years, Nebraska Medicine's BMI guidelines have varied. From no BMI limit to a limit of 40kg/m^2 and the current limit of 35 kg/m^2. Many of these limitations were set based on clinical outcomes and this research was completed to gain a better understanding on the role BMI has on post-kidney transplant outcomes. No association was found between an increased BMI and post kidney transplant outcomes. Therefore, it appears there is no need for a BMI limit however clinical judgment should be made when determining patient's candidacy based on their increased risk factors for new onset diabetes.

The results from this study are also encouraging in the terms of wound care management and prevention at Nebraska Medicine. The lack of association between BMI and wound complications is a positive outcome of this study and the steps to prevent wound complications should be documented and continued in practice as they have proven to be effective. It would also help to share the process taken at Nebraska Medicine with other similar kidney transplant

centers given the majority of research suggesting wound complications in the obese population. These results also suggest an importance of diabetes education. With a trend between BMI and new onset diabetes, it is necessary to inform the diabetes educators of these results to better prepare them for their educations with these patients to help prolong the life of the transplanted kidney since diabetic nephropathy was the leading cause for kidney transplant need in this study.

Research efforts should continue to investigate the effect of BMI, wound complications and new onset diabetes after transplantation relation to kidney transplantation. One aspect of this study that would have been interesting is if there was an association between BMI and longer operating time as many studies suggest longer operating time has an effect on DGF and warm ischemic time.[8.9.10]

A dietitian plays a vital role in evaluating nutritional status prior to kidney transplantation and they can use this data to help prepare and educate patients on the possible outcomes of kidney transplant such as new onset diabetes. The dietitian also bridges the gap between promoting lifestyle change prior to transplant through weight loss counseling, bariatric surgery, and education on BMI levels. However, this is an area in need of more research, specifically concerning weight loss in dialysis patients as a higher BMI has been associated with decreased mortality in this population.

CONCLUSION

We conclude increased BMI is not associated with DGF, but there is a trend between increased BMI and new onset diabetes after transplant. Our study also had a lack of wound complications in patients with a higher BMI unlike similar research in this area. Based off our results there is no indication for BMI limitation, however, clinical judgment needs to be used to determine kidney transplant candidacy. Further research also needs to be completed on the benefits of weight loss over transplantation in patients with a high BMI.

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