Body Mass Index and the Development of New-Onset Diabetes Mellitus or the Worsening of Pre-existing Diabetes Mellitus in Adults After Kidney Transplantation

By

Tysen June Cullen

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CERTIFICATE OF APPROVAL

This is to certify I have read the Master's Thesis of

Tysen June Cullen

and approve the research presented here in

Diane Stadler, PhD, RD, LD

Maureen McCarthy, MPH, RD, LD

John Barry, MD

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LIST OF ABBREVATIONS AND ACRONYMS

BMI	Body Mass Index
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DGR	Delayed Graft Function
DM	Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
$Hgb1_c$	Hemoglobin $A1_c$
HLA	Human Leukocyte Antigen
IL-6	Interleukin-6
IRB	Institutional Review Board
MDRD	Modification of Diet in Renal Disease
NIH	National Institute of Health
NODAT	New-Onset Diabetes Mellitus after Transplant
PAPP-A	Pregnancy-Associated Plasma Protein
UNOS	United Network for Organ Sharing
USRDS	United States Renal Data System

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ABSTRACT

Background:

Kidney transplantation is the preferred treatment for end-stage renal disease (ESRD). Patients who are obese at the time of kidney transplantation are considered to be at increased risk for developing new-onset diabetes mellitus after transplant (NODAT) or worsening of pre-existing diabetes mellitus (DM). This study was designed to determine if these beliefs are true.

Objectives:

1. To determine the relationship between pre-transplant body mass index (BMI) and the development NODAT.
2. To determine the relationship between pre-transplant BMI and the worsening of pre-existing DM in adults after kidney transplantation.

Methods:

Medical records of 204 adults who underwent a first renal transplant at OHSU between August 2008 and February 2011 were reviewed. Patients who received simultaneous organ transplantation who were immunosupressed for non-transplant reasons pr who were less than 18 years of age were excluded. Of the 204 patients assessed, 179 were included in the data analysis. Baseline data were collected at the time of hospital admission immediately before transplantation and included: etiology of ESRD, diagnosis of pre-existing DM, age, sex, ethnicity, weight, height, BMI, plasma creatinine concentration, estimated glomerular filtration rate (eGFR), and type of

induction immunosuppression therapy. Outcome data were collected at the time of hospital discharge and 3, 6, and 12, months after kidney transplantation. Collected data included weight, BMI, DM treatment regimen if indicated, plasma creatinine concentration, eGFR, and type of maintenance immunosupression therapy. Logistic regression was used to determine the relationship between pre-transplant BMI and the development of NODAT at discharge, 3, 6, and 12 months. McNemar's test for correlated proportions was used to assess whether a patient whose DM status worsened during one time interval was likely to continue to worsen in subsequent time intervals. Fisher's test was used to determine if changes in DM treatment following a kidney transplant were related to changes in BMI after transplant.

Results:

1. The cumulative incidence of NODAT at discharge, 3, 6, and 12 months was 14.2%, 19.4%, 20.1%, and 19.4%, respectively.
2. The odds of developing NODAT by discharge, 3, or 6 months after transplant were 1.11 (CI 1.0-1.23), 1.13 (CI 1.03-1.24), and 1.15 (CI 1.05-1.27) per unit increase in pre-transplant BMI.
3. There was a positive association between change in DM treatment from admission to discharge and change in DM treatment from discharge to three months (X_3^2=13.25; p-value = 0.001).

Conclusion:

1. The odds of developing NODAT increased per unit of pre-transplant BMI at discharge, 3 months and 6 months.
2. The development of NODAT is most likely to occur within 3 months of transplantation.
3. The most critical time period for a person with pre-existing DM to experience a worsening of their condition is within the first three months after transplantation.

Chapter 1

Introduction and Significance

Kidney transplantation is the preferred treatment for end-stage renal disease (ESRD). In the United States approximately 16,150 kidney transplants were performed in 2010 and approximately 100 were performed at OHSU[1]. Due to limited availability of donor organs, each transplant center develops a set of standards to evaluate patients for transplant candidacy, including assessment of body mass index (BMI) as a marker of adiposity. There is no universally agreed upon standard for BMI for patients being considered for kidney transplantation. Research to determine characteristics of successful recipients is critical, including assessment of BMI, due to limited organ availability which results in only 10% of kidney transplant candidates receiving a transplant each year. Research suggests that patients with BMI $\geq$ 30 kg/m^2 at the time of transplant are at increased risk of delayed graft function [2], new-onset diabetes mellitus after transplant (NODAT) [3], wound complications[2], increased length of post-surgical hospital stay[4, 5], and decreased survival of the transplanted kidney[6].

The goal of this study was to test the hypothesis that patients who are obese at the time of transplant are more likely to develop NODAT or to experience worsening of pre-existing diabetes mellitus (DM) than patients who are not obese. To accomplish this goal we carried out the following specific aims:

Aim 1: To determine the relationship between pre-transplant BMI and the development of NODAT within 1 year of kidney transplantation.

Aim 2: To determine the relationship between pre-transplant BMI and the worsening of pre-existing DM in adults within 1 year of kidney transplantation. Worsening of pre-existing DM was defined as a change in DM treatment from use of diet and exercise to the use of oral glucose lowering medications, or from the use of oral glucose lowering medication to the use of insulin.

Chapter 2

Background

The aim of this study was to determine if patients with higher body mass index (BMI) at the time of kidney transplant have higher rates of post-transplant complications, specifically new-onset diabetes mellitus after transplant (NODAT) or worsening of pre-existing diabetes mellitus (DM), than patients with lower BMI at the time of transplant. This study analyzed the outcomes among patients who received a kidney transplant at OHSU between August 2008 and February 2011.

Kidney Transplants

Candidates for organ transplantation must undergo rigorous evaluation to identify those with the highest likelihood for successful outcomes. The long-term success rate among kidney transplant recipients has improved over the last three decades due in part to stringent criteria for transplant candidates. However, as the incidence of obesity increases, the complications and comorbidities associated with obesity in kidney transplant patients also increase [7].

Body Mass Index Classifications, Obesity, and other Complications

BMI is an efficient way to describe adiposity by indexing body weight to height [7]. BMI is calculated as the ratio of weight in kilograms divided by height in meters-squared (kg/m^2). The National Institutes of Health (NIH) classifies BMI into six categories: [7]

BMI < 18.5 kg/m^2 - Underweight

BMI of 18.5-24.9 kg/m^2 - Normal Weight

BMI of 25.0-29.9 kg/m^2 - Overweight

BMI of 30-0-34.9 kg/m^2 - Class I Obesity

BMI of 35.0-39.9 kg/m^2 - Class II Obesity

BMI $\geq$ 40.0 kg/m^2 - Class III Obesity

Obesity is a worldwide problem, with 1.6 billion adults classified as overweight and 400 million adults classified as obese[7]. Currently in the United States 30% of the adult population is obese [7] . Increased disease risks parallel the rising obesity rates. Obese individuals are at increased risk for DM, hypertension, hyperlipidemia, cardiovascular disease and chronic kidney disease [8]. These and other comorbidities are associated with higher rates of end-organ dysfunction [9]. DM and hypertension are the two leading causes of ESRD [10]. The number of successful kidney transplant outcomes are reduced by obesity-related comorbidities and altered pharmokinetics [2, 11-14].

There is debate about using BMI to define obesity since it does not take into account the ratio of lean mass to fat mass [4, 5, 15]. Transplant centers may identify a BMI cut-off point based on studies that suggest that patients above that cut-off point are at a higher surgical risk [4]. Complications of kidney transplant surgery associated with higher BMI include post-transplant hospital admission lasting more than 7 days, readmission into the hospital for surgical and metabolic complications, post-operative infection, delayed wound healing including dehiscence (an opening or separation of layers of tissue at the surgical incision site), and urinary leak requiring interventional radiology or additional surgery [6, 15]. Increased adipose tissue and hyperglycemia from insulin resistance put obese patients at higher risk for post-operative infections [11].

Post-transplant weight gain is common in patients, regardless of weight status prior to transplant [16]. Weight gain is multi-factorial and is associated with increased age, lack of physical activity, prior obesity, genetic predisposition or family history, and immunosuppressant drug therapy [17] . Post-transplant patients treated with glucocorticoids often gain weight and experience a redistribution of body fat [16]. DM is a common post-transplant health concern and post-transplant weight gain exacerbates the risk for this condition. In 2002, Meier-Kriesche et al, reported that extremes of very high and very low BMI before kidney transplantation were important risk factors for patient and graft survival [6] .

Delayed graft function (DGF) is defined as the need for dialysis within 7 days of transplnatation [11]. DGF can lead to prolonged length of hospitalization and is considered an important predictor of chronic rejection and reduced transplant survival [4, 5, 15]. According to the United States Renal Data System (USRDS), the risk of DGF increases gradually among patients with BMIs $\geq$ 30 kg/m^2 [1]. Obesity is also related to a higher incidence of cardiovascular disease (CVD). CVD is more common as a cause of death among dialysis patients and kidney transplant patients compared to the general population (OR 1.66) [8, 18].

Weight loss is recommended for overweight and obese transplant candidates [4]. However, weight loss can be even more difficult for those on peritoneal dialysis because of calories absorbed from the peritoneal fluid [9].

Diabetes Mellitus and New-Onset Diabetes After Transplant

DM is the most common etiology of ESRD in the United States[10]. NODAT resembles type 2 DM and is associated with increased age, non-white ethnicity, hepatitis C infection, treatment with glucocorticoids, and chronic use of immunosuppressant medications regimens that include cyclosporine or tacrolimus[19, 20]. Some research suggests that impaired insulin secretion may be the main mechanism for the development of NODAT and that obesity may exacerbate this condition[14]. The literature review at the end of this chapter will summarize the current literature on the relationship between pre-transplant BMI and worsening of pre-existing DM or development of NODAT. Worsening of pre-existing DM was defined as a change in DM treatment from use of diet and exercise to the use of oral glucose lowering medications, or from the use of oral glucose lowering medication to the use of insulin.

Immunosuppressant Medications

Treatment with immunosuppressant medications after kidney transplant reduces the odds of organ rejection. Glucocorticoids are a major component of immunosuppressant therapy; however they cause harm to the insulin-secreting beta cells of the pancreas and indirectly cause weight gain [21]. "Steroid diabetes," or NODAT, was first reported in kidney transplant recipients in 1964, and occurred with a frequency of 40-60% [21]. While glucocorticoids have long been administered to reduce organ rejection, standardized steroid withdrawal protocols are now used to reduce the risk of NODAT[22].

Cyclosporine, introduced in 1983, was the first calcineurin inhibitors approved for use in organ transplant recipients. Calcineurin inhibitors allowed transplant patients to

take lower doses of glucocorticoids and reduced the incidence of NODAT [3, 14, 23-28]. In 1994, tacrolimus, a second-generation calcineurin inhibitor, was approved for use in transplant recipients. However, tacrolimus, when used with glucocorticoids as part of a triple immunosuppressant regimen, was associated with higher rates of NODAT than cyclosporine, despite its steroid-sparing effects [29 30]. As a result, immunosuppressant therapy in combination with the degree of a patient's obesity is considered when selecting patients for kidney transplant candidacy.

Literature Review of Association of BMI and NODAT or the Worsening of Pre-Existing Diabetes in Kidney Transplant Patients.

All of the following publications investigated the associations between pre-transplant BMI and the development of NODAT and are summarized in the Evidnece Table included in Appendix 1. In 2010, Razeghi, et al., published the results of a prospective study of 109 kidney transplant patients. Patients were excluded if they had received a prior transplant or had diabetes at the time of transplant. Patients included in the analysis were followed for 6 months between June of 2003 and May of 2004. Thirty patients (33%) who completed the study developed NODAT. Patients were at increased risk of developing NODAT if they were older than 50 years of age (OR 3.2), were taking a dose of prednisolone $\geq$ 15 mg/day (OR 12.1), were taking a dose of cyclosporine $\geq$ 240 mg/day (OR 40.1), or had ESRD due to polycystic kidney disease (OR 11.8). Patients were at a decreased risk of developing NODAT if they had ESRD due to glomerular nephritis compared to patients who developed ESRD for other reasons (OR 1.4) [3].

Johnston, et al., in 2008, published the results of a retrospective analysis on data collected from the USRDS on the association between the use of sirolimus after transplantation and the development of NODAT. There were 20,124 adult patients who received their first kidney transplant and who did not have ESRD due to diabetes at the time of transplant. Participants were followed for an average of 2.63 years post transplant. Patients treated with sirolimus were at increased risk for developing NODAT when used independently or in combination with cyclosporine (adjusted hazard ratio 1.61), tacrolimus (adjusted hazard ratio 1.66), or an antimetabolite (adjusted hazard ratio 1.36) compared to patients who were not treated with sirolimus [20].

Shehab-Eldin, et al., in 2008 published the results of a prospective cross-sectional study of kidney transplant patients to identify risk factors for the development of NODAT. Fifty-five patients were followed for 15 ± 4 months. Patients were divided into two groups: those with normal blood glucose conentations (n=34) and those with impaired fasting glucose (n=21) before kidney transplant. Fasting insulin, pro-insulin, and adiponectin concentrations were measured, and insulin resistance beta-cell function was calculated and correlated with the development of NODAT. NODAT developed in 11.8% and 19% of those with normoglycemia and impaired fasting glucose, respectively. The authors concluded that a baseline fasting insulin level of 54.54 mU/I predicted the development of NODAT with a specificity of 95.5% and was the only significant factor in the multivariate analysis [23].

Bayes, et al., conducted a prospective study to determine the correlation between pre-transplant plasma adiponectin concentrations and NODAT. One hundred and ninty-nine non-diabetic patients (128 males, with an average age of 53 ± 11 years, and an

average BMI of 25 ± 3.8 kg/m^2) were included in the analysis. Fasting plasma glucose, insulin, adiponectin, C-reactive protein (CRP), interleukin-6 (IL-6) and pregnancy-associated plasma protein A (PAPP-A) were measured before and after kidney transplant. Forty-five patients (22.6%) developed NODAT; of whom 77.3 % were diagnosed within 3 months of transplantation. Patients who developed NODAT had a higher average pre-transplant BMI (26.6 ± 4.3 kg/m^2) compared to patients who did not develop NODAT (24.5 ± 3.5 kg/m^2, p = 0.005). Patients with NODAT had lower adiponectin concentrations (11.3 ± 5.0 µg/ml vs. 16.3 ± 6.5 µg/ml, p < 0.001) and higher CRP concentrations (6.11 mg/L vs. 3.4 mg/L, p = 0.032) than patients who did not develop NODAT. Multivariate logistic regression and Cox analysis showed that use of tacrolomis as a CNI, pre-transplant BMI, and pre-transplant adiponectin concentrations were predictors of NODAT. Receiver operating characteristic curve analysis showed that an adiponectin concentration of 11.4 mg/L was negatively associated with the risk of developing NODAT. Of the inflammatory markers studied, adiponectin was the only independent predictor of NODAT [24].

Hur, et al., performed a prospective study to analyze the incidence of NODAT and to investigate factors contributing to the incidence of NODAT. Seventy-seven patients completed a glucose tolerance test one week before transplantation and 1 year and 7 years after transplantation. Of the 77 patients, 38 (23.3%) did not develop NODAT within the 7 years of the study. Twelve patients (15.5%) developed NODAT by 1 year and then recovered by 7 years post-transplant. Nine patients (11.6%) developed NODAT by 7 years but did not have diabetes at one year. Eighteen patients (23.6%) developed diabetes at 1 year and still had diabetes at 7 years following their transplant. Older age (≥

40 years of age) was a predictor for NODAT at one year and higher BMI ($\geq$ 25 kg/m^2) was a predictor of NODAT at 7 years [14].

Joss, et al., performed a retrospective review of 787 patients who received a kidney transplant between 1994 and 2004. NODAT was diagnosed in patients who had two random plasma glucose concentrations >11.1 mmol/L (200 mg/dL) after the first month post-transplant or in patients who required treatment for hyperglycemia within the first month and continued treatment thereafter. Risk factors for the development of NODAT were older age, heavier weight at time of transplantation ($\geq$ 75 kg), higher pre-transplant random plasma glucose concentrations, higher plasma glucose within the first seven days post-transplant, and use of tacrolimus. The incidence of NODAT at 1 year post-transplant was 7.7%. The incidence of NODAT requiring either insulin or oral hypoglycemic agents was 4.5%. Ten-year patient survival was, 81.9% for those without diabetes, 67.1% in patients with NODAT and 65.3% in patients who had diabetes before transplant. There were no significant differences in graft survival rates between those who developed NODAT and those who did not [25].

Schiel, et al., followed patients with ESRD but without DM who received a kidney transplant at a single center beginning in 1992. Two-hundred and fifty-three patients were studied with an average age of 52.2 ± 12.6 years, an average BMI of 22.0 ± 7.9kg/m^2, and an average follow up duration of 3.3 ± 1.6 years. Forty-three patients (17%) developed NODAT. Patients with NODAT were significantly older (55.9 ± 12.5 vs. 50.3 ± 11.4 years) and had a higher average BMI (24.0 ± 8.5 vs 21.6 ± 7.8kg/m^2) than those who did not develop NODAT. There were no differences between the groups with

respect to blood pressure control or frequency and dosage of immunosuppressant drugs such as cyclosporine, tacrolimus, and sirolimus during the follow-up [26].

Kasiske, et al., retrospectively analyzed data of 11,659 patients from the USRDS. Patients were Medicare beneficiaries who received their first kidney transplant between 1996–2000. The goal of this study was to investigate immunosuppressant therapies and their impact on NODAT. The cumulative incidence of NODAT was 9.1%, 16.0%, and 24.0%, at 3, 12, and 36 months post-transplant, respectively. Using Cox's proportional hazards analysis, risk factors for NODAT included age, African-American race, Hispanic ethnicity, male kidney donor, increasing human leukocyte antigen (HLA) mismatches, hepatitis C infection, body mass index $\geq$30 kg/m^2, and use of tacrolimus as the initial maintenance immunosuppressant medication[30].

Parikh, et al., conducted a retrospective analysis of medical records to determine if obesity impacted development of NODAT in patients who received a kidney transplant from January 1998 until March 2001. Three-hundred kidney transplants were performed and 40% (n=120) had ESRD due to DM. The 180 patients (60%) who did not have DM prior to transplant surgery were followed post-transplant and 18 cases (10%) of NODAT were identified; 72% of the cases developed NODAT within the first 2 months after transplant and 38% required insulin for glucose control. Controls (n=36) were matched to the NODAT cases for immunosuppressant regimen, gender, and type of donor. BMI was significantly associated with NODAT (adjusted OR 1.22) after controlling for number of rejections, age, and other factors. Obesity, defined as BMI $\geq$30 kg/m^2, was an independent predictor of NODAT [28].

Miles, et al., performed a prospective study of the effects of NODAT on long-term (9.5 ± 1.3 year) graft survival. Seventy-eight patients were studied and 40 developed NODAT (51.1%). There was 48% graft survival in NODAT cases and 70% graft survival in controls after 12 years. NODAT was a significant predictor of graft loss independent of age, sex, and race [21].

Controversy remains about the causes of NODAT and how obesity contributes to higher rates of NODAT. This study investigated the relationship between pre-transplant BMI as a continuous variable and the development of NODAT and the worsening of pre-existing diabetes mellitus after kidney transplantation.

Chapter 3

Methods

General Design

A retrospective study design was used to determine the relationship between body mass index (BMI) and the development of new-onset diabetes mellitus after transplant (NODAT) or worsening of pre-existing diabetes mellitus (DM) within 1 year of kidney transplantation. This study was reviewed and approved by the Oregon Health & Science University (OHSU) Institutional Review Board (IRB) before data abstraction from the medical records was performed.

Subjects and Settings

Medical records of 204 adults who underwent a first renal transplant at OHSU between August 2008 to February 2011 were reviewed. Patients who received simultaneous transplantation with another organ, who were immunosuppressed for non-transplant reasons, or were not at least 18 years of age were excluded. This resulted in a sample size of 179.

Data Collection

All data were obtained from the OHSU Electronic Medical Record System (OHSU-EMRS). Baseline data at the time of hospital admission for the kidney transplant included age, gender, ethnicity, weight, height, BMI, etiology of end-stage renal disease (ESRD), type of dialysis, diagnosis of pre-existing diabetes mellitus (DM) and medications used to treat the condition, plasma creatinine concentration, eGFR, and type

of induction immunosuppressant medication used when pertinent. The etiology of ESRD was obtained from the 2728 Medicare Form 538.1.

Outcome data collected at the time of hospital discharge and 3, 6, and 12 months after kidney transplantation included weight, BMI, maintenance immunosuppressant therapy, pre-existing DM treatment regimen, or a new diagnosis of NODAT, plasma creatinine concentration, eGFR, post-transplant dialysis status, duration of hospital admission, and delayed graft function or graft failure which was defined as the need for maintenance dialysis. The components of maintenance immunosuppressant therapy (tacrolimus, prednisone, and cyclosporine) were collected because of their effect on insulin production and cellular insulin resistance. DM treatment regimen was identified as: diet and exercise, oral medication, and insulin with or without oral medication. Changes in the levels of DM treatment regimen were used to indentify worsening, no change, or improvement of DM treatment from one consecutive time interval to another. Worsening of pre-existing DM was defined as a change in DM treatment from use of diet and exercise to the use of oral glucose lowering medications, or from the use of oral glucose lowering medication to the use of insulin. If a patient had a new diagnosis of NODAT on their discharge summary or their 3, 6, & 12 month follow up summary, it was confirmed by identifying the patient's NODAT treatment regimen. Information about the donated kidney included the donor-to-recipient relationship: defined as living-related kidney transplant, living-unrelated kidney transplant, or deceased-donor kidney transplant.

Anthropometric Measurements

Weight at admission was measured in light clothing using a stand-on scale with digital display (Scale-Tronix Model 5004, Wheaton IL) to the nearest 0.01 kg. Height, without shoes, was measured using a wall-mounted stadiometer (Harpenden Stadiometer, Holtain Ltd, Crymych, UK) and was recorded to the nearest 0.01 cm. Body mass index (BMI) was calculated as the patient's weight in kilograms, divided by his or her height in meters-squared.

Blood Sample Collection and Analysis

Blood samples were collected from a peripheral arm vein by venipuncture using sterile technique. Blood samples were collected into 10 mL heparinized tubes and sent to the OHSU Clinical Chemistry Laboratory for analysis of plasma creatinine concentration using the Jaffe's method[31].

Calculations

GFR was estimated using the Modification of Diet in Renal Disease eGFR equation which includes plasma creatinine concentration, age, race, and gender [32].

Data management

Data were de-identified for each participant and recorded in an electronic Microsoft Access data base. The Microsoft Access data base was exported to an Excel database and imported into STATA for statistical analysis. All endpoint data were verified by visually comparing database contents with the source form. Data were

maintained electronically on an OHSU hard drive which was backed up daily and archived off-line on a daily, weekly, monthly, and yearly basis.

Confidentiality

Participant confidentiality was protected by using a unique study identifier on all forms and in all data sets, and by ensuring that data were stored only on computers secured by password access. Paper forms with the unique identifier were kept in locked storage in Gaines Hall Room 212 on the OHSU campus. All participant information was considered confidential. Confidentiality was assured in this study through several mechanisms. First, each participant was assigned a unique study identifier which was used on all study forms. Second, all study forms, and paper records that contained participant information were kept in a secured, locked area when not in use. In addition, such materials, when in use, were kept away from public scrutiny. Third, access to all participant data and information, including laboratory specimen results, was restricted to authorize personnel. In the case of computerized information, access to the study data on computers was password protected. In addition, study personnel were required to sign a confidentiality statement affirming that they agreed to abide by the OHSU's policies on research confidentiality and ethics. Finally, patients were not identified by name in any reports nor were data presented in such a way that the identity of individual participants could be inferred.

Statistical Analysis

STATA, Version 11.0 (StataCorp, College Station, TX.), was used to analyze the data. Descriptive statistics were used to characterize the sample. Means and standard deviations as well as frequencies and percentages were used to compare the outcome data collected. Logistic regression was used to determine the relationship between pre-transplant BMI at admission (a continuous variable) and the development of NODAT (a dichotomous variable) at specified times within 1 year of kidney transplantation. Patient age (continuous variable), gender (binary variable), immunosuppressant regimen (categorical variable), and etiology of ESRD (categorical variable) were included in the model as independent variables. Regression models were constructed individually given the patient's diabetes mellitus status at the time of discharge and at 3, 6 and 12 months after transplant.

Logistic regression was also used to assess the association between pre-transplant BMI and the development NODAT. These models were constructed individually using pre-transplant BMI and the development of NODAT by discharge, 3, 6, and 12 months. To evaluate the appropriateness of using pre-transplant BMI as a contraindication for kidney transplantation, fitted logistic regression models were developed using pre-transplant BMI as a continuous variable. These were used to identify thresholds of BMI that predicted the odds developing of NODAT.

Patients with pre-existing DM at the time of transplant were assessed based on changes in the type of treatment used to control DM after transplant. Patients were categorized into one of three levels described under data collection. McNemar's test for correlated proportions was used to assess whether a patient whose diabetes status

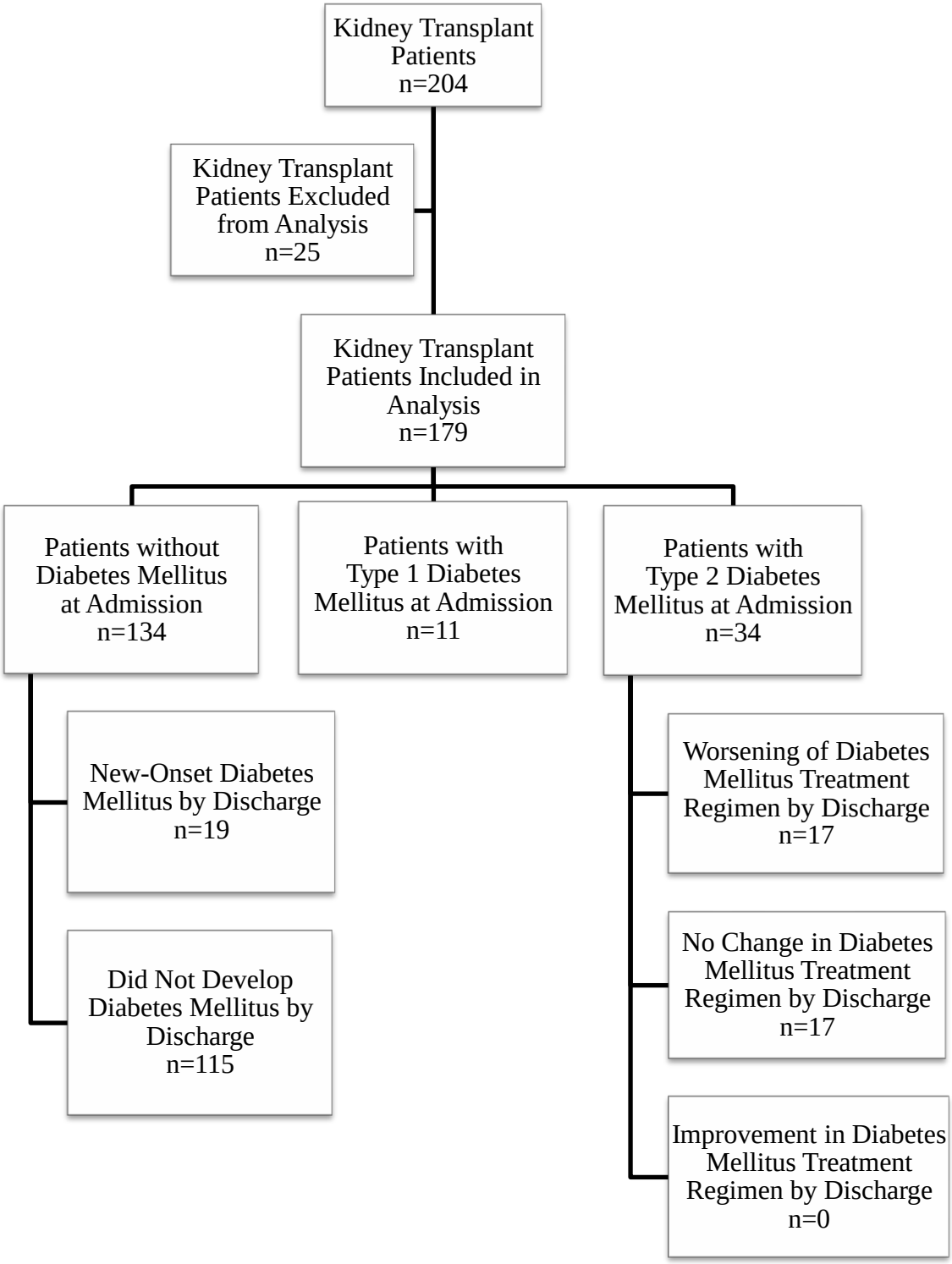
worsened during one time interval (e.g., discharge to 3 months) was likely to continue to worsen during subsequent time intervals (e.g., 3 months to 6 months)[33]. Fisher's exact test was used to determine if change in pre-existing DM treatment regimen following a kidney transplant was related to changes in BMI after transplant.

Chapter 4

Results

A retrospective review of medical records of all adult kidney transplant recipients, who received a primary kidney transplant between August 2008 and February 2011 at OHSU, was performed to determine if body mass index (BMI) at the time of transplant was associated with an increased risk for developing new-onset diabetes mellitus after transplant (NODAT) or worsening of pre-existing type 2 diabetes mellitus (DM) after transplant. Two hundred and four medical records were reviewed (see Figure 1), from which information from 25 of the kidney transplant recipients (12.3%) was excluded. Reason for exclusion included: 7 patients (3.4%) were lost to follow up within 12 months of transplant, 7 patients (3.4%) received immunosuppressant therapy before transplant for reasons other than the scheduled kidney transplant, 5 patients (2.5%) had received a previous kidney transplant, 4 patients (2.0%) died with a functioning graft within 12 months of transplant, 1 patient (0.5%) had acute rejection of the transplanted kidney and lost the graft within 3 days of the transplant, and 1 patient (0.5%) had chronic rejection of the transplanted kidney and the graft was lost within three months of transplant. Of the remaining 179 patients included in the analysis, 134 (74.9%) did not have DM prior to kidney transplantation, 11 (6.1%) had type 1 DM prior to transplantation, and 34 (13.4%) had type 2 DM prior to transplantation. Of the patients who did not have DM prior to transplantation, 19 (14.2%) developed NODAT by hospital discharge. Of the patients who had type 2 DM prior to transplantation, 17 (50%) required more intensive treatment for their DM treatment by the time they were discharged after transplantation.

Figure 1. Distribution of Adult Kidney Transplant Patients Based on Presence of Diabetes Mellitus at Admission and Change in Diabetes Mellitus Status or Treatment Regimen At Discharge.



Patient Characteristics at Admission

Baseline characteristics of the 179 kidney transplant patients who met the inclusion criterion for analysis are presented in Table 1. Sixty-five percent were male, 78.7% were white, non-Hispanic, and the average (± SD) age was 50.9 ± 14.4 years. Type 2 DM (16.8%), polycystic kidney disease (15.6%), and hypertension (14.5%) were the most common etiologies of end-stage renal disease (ESRD). Of the study participants 29.6%, had an etiology of ESRD categorized as "other" which included glomerulonephritis, reflux nephropathy, focal glomerulosclerosis, or kidney disease secondary to another illness such as meningococcal meningitis. The most frequently used induction immunosuppressant medications were daclizumab (53.6%) and anti-thymocyte globulin (29.1%). The majority of donor kidneys, 53.6%, were obtained from living donors. Tacrolimus and prednisone were used in combination for 99.4% of patients as their maintenance immunosuppressant regimen after kidney transplant and the average length of stay was 7.4 ± 3.0 days (data not shown). On average, kidney function improved significantly immediately after kidney transplantation as shown by a mean percent increase in eGFR of 609% and a mean percent decrease in plasma creatinine concentration of 74% by discharge (Table 2).

Table 1. Characteristics of Adult Kidney Transplant Patients at Admission*.

	Total n=179	Males n=117	Females n=62
Age (years)			
< 20	5 (2.8)	1 (0.9)	4 (6.5)
20-30	14 (7.8)	7 (6.0)	7 (11.3)
30-40	23 (12.9)	17 (14.5)	6 (9.7)
40-50	31 (17.3)	21 (18.0)	10 (16.1)
50-60	56 (31.3)	40 (34.2)	16 (25.8)
> 60	50 (28.0)	31 (26.5)	19 (30.7)
Race/ Ethnicity			
White/ non-Hispanic	141 (78.8)	91 (77.8)	50 (80.7)
Asian/ non-Hispanic	17 (9.5)	10 (8.6)	7 (11.3)
Black/ non-Hispanic	8 (4.5)	7 (6)	1 (1.6)
Hispanic	7 (3.9)	3 (2.6)	4 (6.5)
Other	6 (3.4)	6 (5.1)	0 (0)
Etiology of End-Stage Renal Disease			
Type 1 Diabetes Mellitus	11 (6)	6 (5.1)	5 (8.1)
Type 2 Diabetes Mellitus	29 (16.2)	22 (18.8)	7 (11.3)
Hypertension	26 (14.5)	20 (17.1)	6 (9.7)
Polycystic Kidney Disease	28 (15.6)	12 (10.3)	16 (25.8)
IgA Nephropathy	18 (10.1)	15 (12.9)	3 (4.8)
Unknown	14 (7.8)	8 (6.8)	6 (9.7)
Other	53 (29.6)	34 (29.1)	19 (30.7)
Diabetes Mellitus Status			
No Diabetes	134 (75)	87 (74.4)	47 (75.8)
Diabetes Mellitus Type 1	11 (6)	6 (5.1)	5 (8.1)
Diabetes Mellitus Type 2	34 (19)	24 (20.5)	10 (16.1)
Induction Immunosuppressant			
No Induction	3 (1.7)	2 (1.7)	1 (1.6)
Basiliximab	28 (15.6)	20 (17.1)	8 (13)
Daclizumab	96 (53.6)	63 (53.9)	33 (53.2)
Anti-Thymocyte Globulin	52 (29.1)	32 (27.4)	20 (32.3)
Type of Kidney Donation			
Living Related	46 (25.7)	24 (20.5)	22 (35.5)
Living Unrelated	50 (27.9)	38 (32.5)	12 (19.4)
Deceased-Donor Kidney Transplant	83 (46.6)	55 (47.0)	28 (45.2)

* Data reported frequencies and (percentages).

Table 2. Estimated Mean (± SD) Glomerular Filtration Rate and Plasma Creatinine Concentration at Admission and Discharge in Adult Kidney Transplant Patients.

	Total n=179	Males n= 117	Females n=62
Estimated Glomerular Filtration Rate (ml/min/1.73 m^2)			
Admission	8.7 ± 4.2	8.6 ± 4.1	9.0 ± 4.5
Discharge	49.7 ± 19.6	46.9 ± 19.5	54.9 ± 18.6
Plasma Creatinine Concentration (mg/dL)			
Admission	7.6 ± 3.5	8.3 ± 3.6	6.4 ± 3.0
Discharge	1.7 ± 1.0	1.9 ± 1.0	1.2 ± 0.6

Body Mass Index

The average pre-transplant BMI for all kidney transplant patients was 27.3 ± 4.8 kg/m^2 as displayed Figure 2 and Table 3. Males exhibited a slightly higher BMI (27.9 ± 4.4 kg/m^2) than females (26.2 ± 5.3 kg/m^2). The difference in mean pre-transplants BMI between males and females was 1.78 kg/m^2 (95% CI of difference in BMI: 0.30-3.25 kg/m^2; p-value = 0.02). Pre-transplant BMI was more symmetrically distributed among males than among females and the BMI distribution curve for females was skewed slightly to the right.

The distribution of BMI by weight category at admission and 3, 6, and 12 months after kidney transplantation is presented in Table 3. At admission BMI was evenly distributed among the normal weight (18.5-24.9 kg/m^2), overweight (24.5-29.9 kg/m^2), and Class 1 Obesity (30.0-34.9 kg/m^2) classifications. Only 6 patients, 3.4%, had a BMI $\geq$ 35.0 kg/m^2 and of those, 50% were male. At 3, 6, and 12 months after transplantation, the number of patients who had a BMI $\geq$ 35.0 kg/m^2 increased to 14 (7.8%), 24 (13.4%),

and 27 (15.1%), respectively. The number of male patients in the Class 2 Obese category (35.0-39.9 kg/m^2) increased 4.6 times (from 3 to 14 patients) and the number of female patients increased 5 times (from 2 to 10 patients), from admission to 12 months. There were more male patients in the overweight category (24.5-29.9 kg/m^2); female patients were more consistently in the normal weight category (18.5-24.9 kg/m^2) throughout the 12 months of follow up.

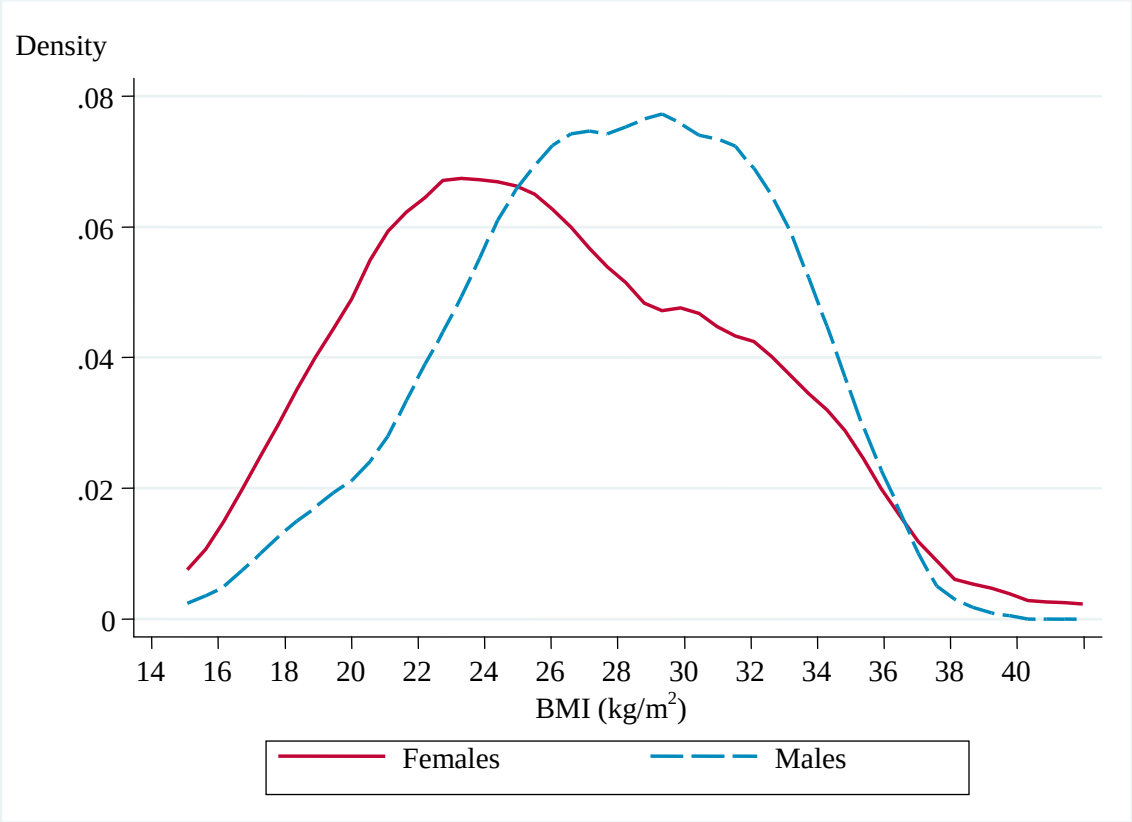


Figure 2. Smooth density histogram of pre-transplant body mass index (BMI) of male (dashed) and female (solid) adult kidney transplant patients. The distribution curve was shifted 1.78 kg/m^2 (95% CI: 0.30—3.25 kg/m^2; p value = 0.02) for males (27.9 ± 4.4 kg/m^2) compared to females (26.2 ± 5.3 kg/m^2). The BMI distribution was more symmetrically distributed for males than for females; the female distribution curve was skewed to the right.

Table 3. Categorical Distribution of Body Mass Index by Weight Classifications among Adult Kidney Transplant Patients at Admission and 3, 6, and 12 Months after Transplantation*.

Body Mass Index (kg/m^2)	Total n=179	Males n= 117	Females n=62
Admission	27.3 ± 4.9	27.9 ± 4.4	26.2 ± 5.3
< 18.5	5 (2.8)	2 (1.7)	3 (4.8)
18.5-24.9	57 (31.8)	29 (24.8)	28 (45.2)
25.0-29.9	57 (31.8)	42 (35.9)	15 (24.2)
30-0-34.9	54 (30.2)	41 (35.0)	13 (21.0)
35.0-39.9	5 (2.8)	3 (2.6)	2 (3.2)
> 40.0	1 (0.6)	0 (0)	1 (1.6)
Three Months	28.0 ± 4.8	28.4 ± 4.4	27.2 ± 5.6
< 18.5	2 (1.1)	1 (0.9)	1 (1.6)
18.5-24.9	49 (27.4)	25 (21.4)	24 (38.7)
25.0-29.9	63 (35.2)	46 (39.3)	17 (27.4)
30-0-34.9	51 (28.49)	38 (32.5)	13 (21.0)
35.0-39.9	14 (7.8)	7 (6.0)	7 (11.3)
> 40.0	0 (0)	0 (0)	0 (0)
Six Months	28.8 ± 5.1	29.3 ± 4.7	27.9 ± 5.9
< 18.5	2 (1.2)	1 (0.9)	1 (1.6)
18.5-24.9	42 (23.5)	20 (17.1)	22 (35.5)
25.0-29.9	64 (35.8)	45 (38.5)	19 (30.7)
30-0-34.9	47 (26.3)	36 (30.8)	11 (17.7)
35.0-39.9	21(11.7)	14 (12.0)	7 (11.3)
> 40.0	3 (1.7)	1 (0.9)	2 (3.2)
Twelve Months	28.8 ± 6.0	28.9 ± 6.0	28.6 ± 6.2
< 18.5	5 (2.8)	3 (2.6)	2 (3.2)
18.5-24.9	40 (22.4)	20 (17.1)	20 (32.3)
25.0-29.9	56 (31.3)	44 (37.7)	12 (19.4)
30-0-34.9	51 (28.5)	35 (30.0)	16 (25.8)
35.0-39.9	24 (13.4)	14 (12.0)	10 (16.1)
> 40.0	3 (1.7)	1 (0.9)	2 (3.2)

* Data reported as means ± SD and frequencies and (percentages).

Body Mass Index and the Development of New-Onset Diabetes Mellitus

Table 4 provides information about the 134 patients who did not have DM at admission. Of these patients, 14.2% were diagnosed with NODAT by discharge. The cumulative incidence of NODAT at 3, 6, and 12 months after kidney transplantation was 19.4%, 20.1%, and 19.4%, respectively. Of the patients who developed NODAT most were classified as Class 1 Obese (30.0-34.9 kg/m^2) before transplantation and at discharge, 3, 6, and 12 months. Of the patients who did not develop NODAT within 12 months of kidney transplantation, most were classified as normal weight (18.5-24.9 kg/m^2) before transplantation and at discharge, 3, 6, and 12 months.

Table 4. Distribution by Category of Body Mass Index at Admission for Adult Kidney Transplant Patients (n=134) Who Did or Did Not Have New-Onset Diabetes After Transplant by Discharge, 3, 6, or 12 Months*.

Body Mass Index (kg/m^2)	Discharge	Three Months	Six Months	Twelve Months
New-Onset Diabetes After Transplant	n=19	n=26	n=27	n=26
< 18.5	0 (0)	0 (0)	0 (0)	0 (0)
18.5-24.9	5 (26.3)	5 (19.2)	5 (18.5)	4 (15.4)
25.0-29.9	5 (26.3)	8 (30.8)	9 (33.3)	8 (30.8)
30-0-34.9	7 (36.8)	11 (42.3)	11 (40.7)	11 (42.3)
35.0-39.9	2 (10.5)	2 (7.7)	2 (7.4)	3 (11.5)
> 40.0	0 (0)	0 (0)	0 (0)	0 (0)
No Diabetes Mellitus	n=115	n=108	n=107	n=108
< 18.5	4 (3.4)	4 (3.7)	4 (3.7)	4 (3.7)
18.5-24.9	44 (38.3)	44 (40.7)	44 (41.1)	45 (41.7)
25.0-29.9	35 (30.4)	32 (29.6)	31 (30.0)	32 (29.6)
30-0-34.9	29 (25.2)	25 (23.1)	25 (23.4)	25 (23.1)
35.0-39.9	2 (1.5)	2 (1.9)	2 (1.9)	1 (0.9)
> 40.0	1 (0.8)	1 (0.9)	1 (0.9)	1 (0.9)

*Data presented as frequencies and (percentages).

The relationship between pre-transplant BMI and the development of NODAT by discharge, 3, 6, or 12 months after transplantation was assessed using logistic regression with BMI treated as a continuous variable rather than a categorical variable (Table 5). This alternative analysis was done because too few participants who developed NODAT had BMIs in the higher weight categories to allow modeling of this variable as categorical. At discharge, 3 and 6 months after transplantation, the interaction between BMI and sex was not significant (p-value = 0.753, 0.550, 0.362, respectively) although BMI was significant (p-value = 0.046, 0.013, 0.004, respectively), suggesting a common effect of BMI on the odds of developing NODAT for both sexes. The odds of developing NODAT by discharge, 3, or 6 months after transplant were 1.11 (CI 1.0-1.23), 1.13 (CI 1.03-1.24), and 1.15 (CI 1.05-1.27) per unit increase in pre-transplant BMI, respectively.

At discharge and 3 months after transplant, sex had no significant effect on a patient's odds of developing NODAT (p-value = 0.14, 0.21) (Figure 3A, B). At six months after transplant the odds of developing NODAT among females was 2.62 times higher than the odds of a developing NODAT among males at any given BMI and was significant (p-value=0.04) (Figure 3C).

At 12 months the interaction between sex and BMI was significant (p-value = 0.079) for predicting the odds of developing of NODAT. Because of this interaction, the results from the model are summarized separately for males and females (Figure 3D). For males the odds of developing NODAT by 12 months post-transplant increased 34% for each unit increase in pre-transplant BMI and was significant (p-value = 0.002). For females, the odds of developing NODAT by 12 months post-transplant increased 10% for each unit increase in pre-transplant BMI but was not-significant (p-value = 0.144).

Table 5. Relationships among Body Mass Index (BMI) at Admission, Sex, and the Development of New-Onset Diabetes After Transplant (NODAT) at Discharge, 3, 6, and 12 months (n=134).

				Odds Ratio for Developing NODAT (95% CI)	
	Interaction (p-value)	Body Mass Index (p-value)	Sex (p-value)	Body Mass Index (kg/m^2) (adjusted for Sex)	Sex* (adjusted for BMI)
Discharge	No (0.753)	Yes (0.046)	No (0.14)	1.11 (1.00--1.23)	2.17 (0.79--5.97)
3 months	No (0.550)	Yes (0.013)	No (0.21)	1.13 (1.03--1.24)	1.79 (0.72--4.49)
6 months	No (0.362)	Yes (0.004)	Yes (0.04)	1.15 (1.05--1.27)	2.62 (1.04--6.58)
12 months	Yes (0.079)	-	-	-	-
Females (n=47)		No (0.144)	-see text-	1.10 (0.97--1.24)	-see text-
Males (n=87)		Yes (0.002)		1.34 (1.12--1.61)	

*Odds ratio for developing NODAT (females relative to males)

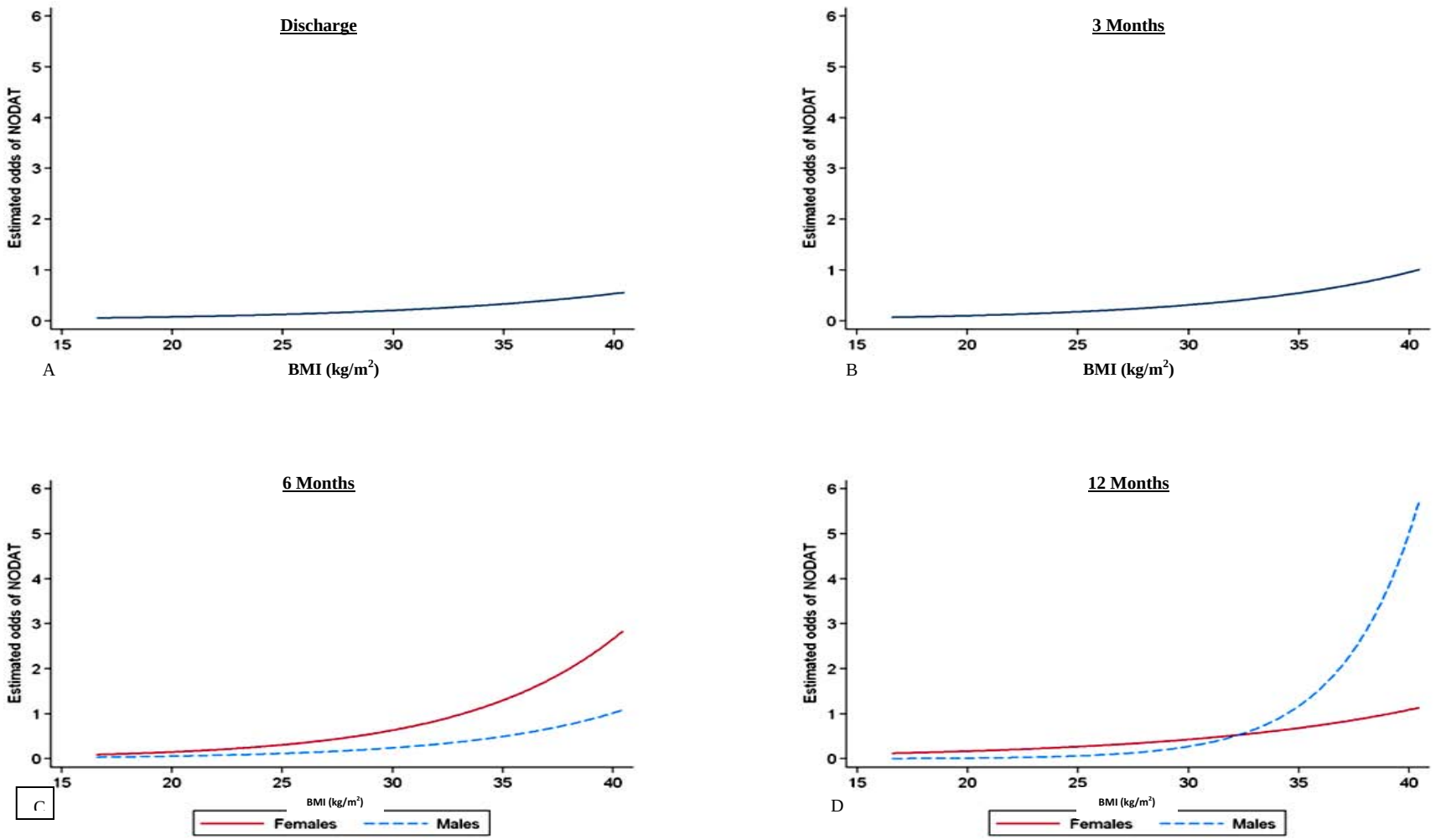


Figure 3. Pre-transplant Body Mass Index (BMI), Sex, and the Odds of Developing of New-Onset Diabetes After Transplant (NODAT) at Discharge, 3, 6, and 12 months (n=134).

To better illustrate the interaction effect, the odds of developing NODAT (females relative to males) were estimated at pre-transplant BMIs of 25 kg/m^2, 30 kg/m^2, and 35 kg/m^2 (Figure 4). At a pre-transplant BMI of 25 kg/m^2, the odds of developing NODAT among females was 4.23 times higher than the odds of developing NODAT among males and the difference was significant (95% CI:1.09-16.38; p-value = 0.037). At a BMI of 30 kg/m^2, the odds of developing NODAT among females was 1.56 times higher than the odds of developing NODAT for males, but was not significant (95% CI:0.58-4.25 p-value = 0.357). At a BMI of 35 kg/m^2, the odds of developing NODAT for females is 0.58 times lower than the corresponding odds of developing NODAT for males, but this was not significant (95% CI: 0.12-2.91; p-value = 0.5.) Although interesting, these results have to be interpreted with caution because of the low number of patients who had a pre-transplant BMI $\geq$ 35 kg/m^2.

There were no differences between the patients who developed NODAT and those that did not with respect to age, ethnicity, type of maintenance immunosuppressant regimen, etiology of ESRD, length of stay, and the development of NODAT at discharge and 3, 6, and 12 months (data not shown).

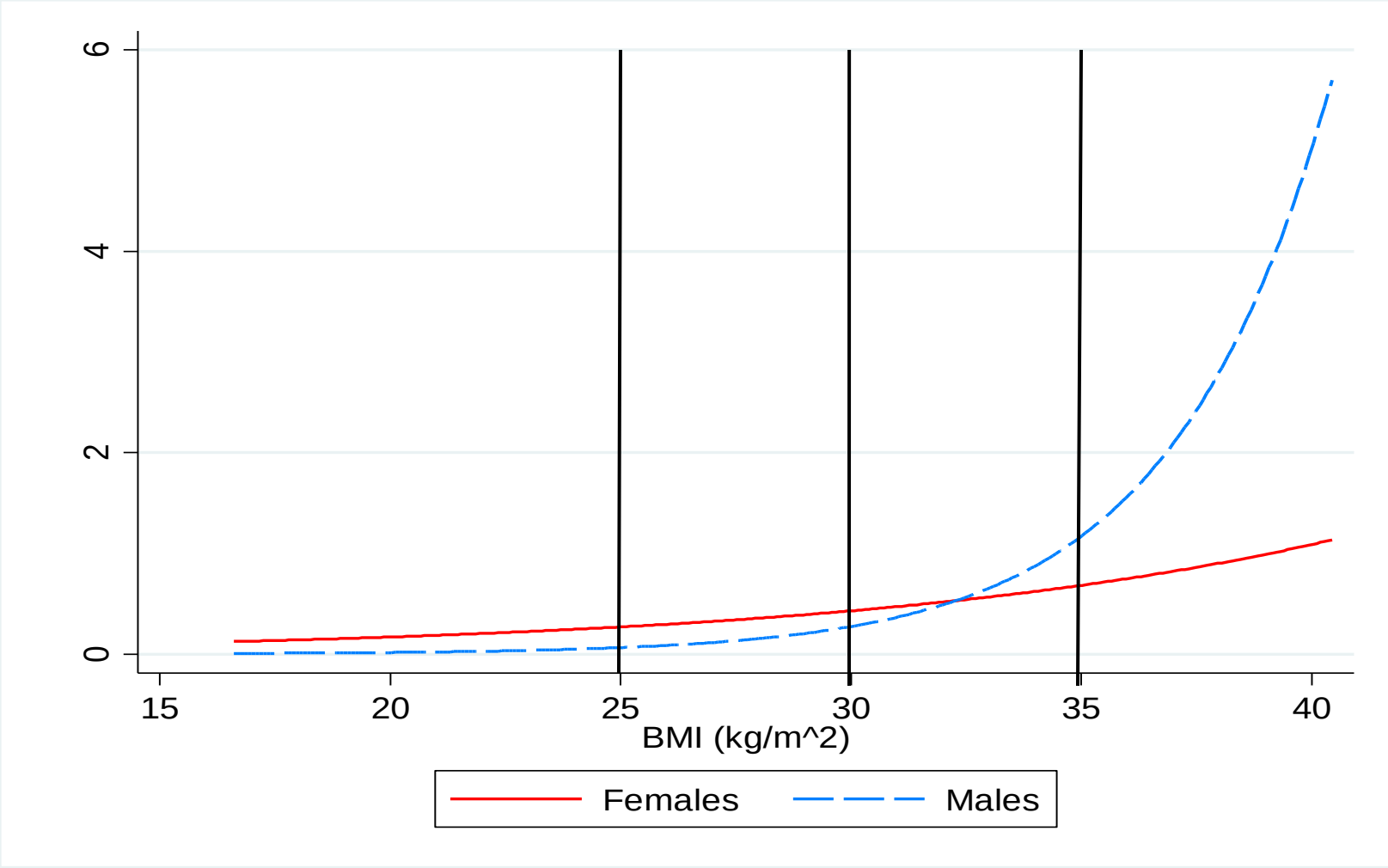


Figure 4. Pre-Transplant Body Mass Index (BMI) by Categories, Sex, and the Odds of Developing New Onset Diabetes After Transplant (NODAT) at 12 months (n=134).

The Relationship between Body Mass Index and Change in Treatment of Pre-existing Diabetes Mellitus in Adult Kidney Transplant Patients within 12 Months of Transplantation.

The 34 patients (19%) who presented with Type 2 DM at admission for kidney transplant were analyzed to determine the impact of kidney transplantation on change in DM treatment regimen within one year of transplant (Table 6). The average BMI and age of this subgroup was 29.3 ± 4.2 kg/m^2 and 57.2 ± 9.4 years, respectively. The majority, 65%, was white, non-Hispanic; 85% had ESRD as a result of Type 2 DM.

Table 6. Distribution by Weight Classification Category of Body Mass Index at Admission of Adult Kidney Transplant Patients with Type 2 Diabetes Mellitus*.

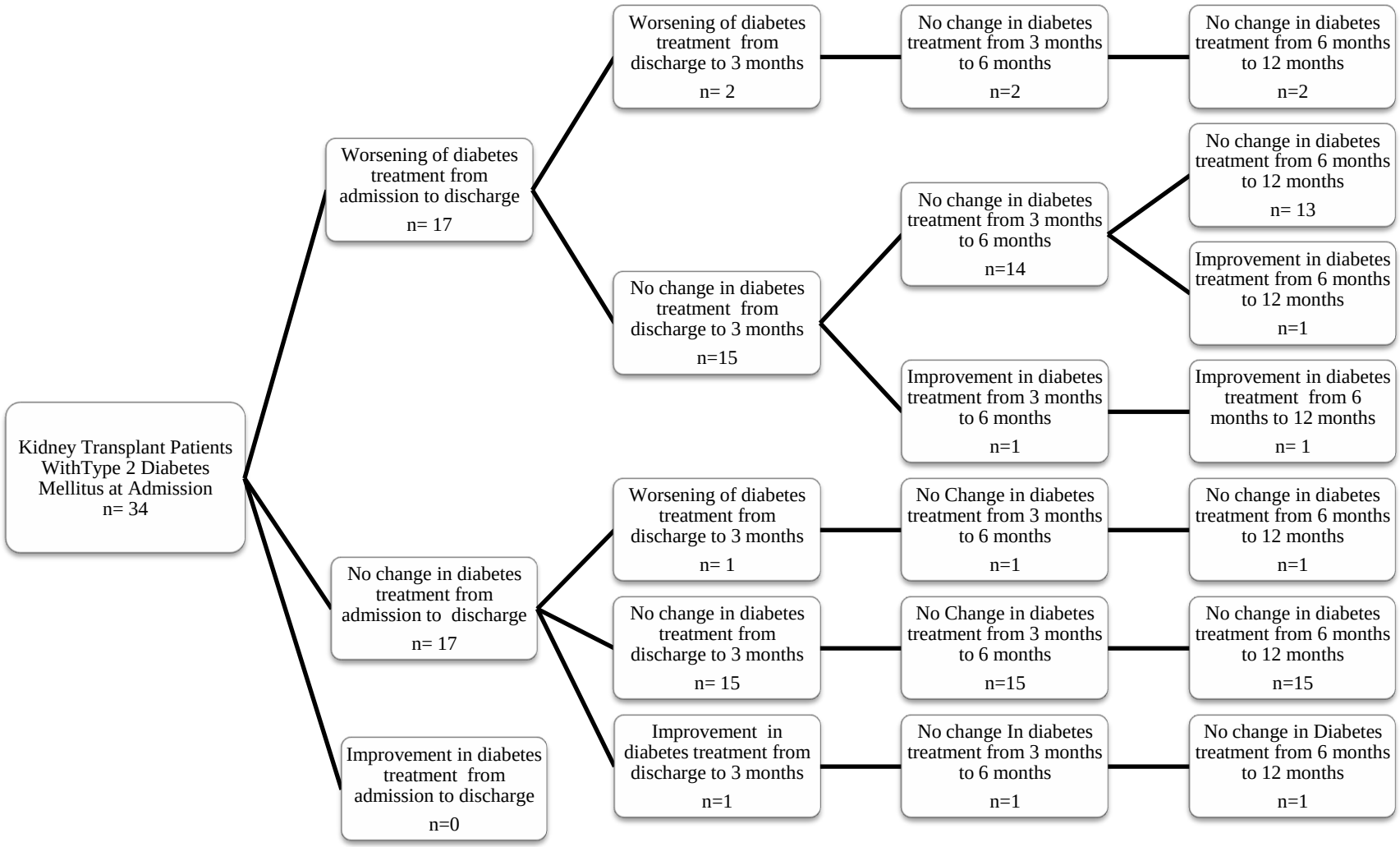
Body Mass Index (kg/m^2)	Total n=34	Males n=24	Females n=10
	29.3 ± 4.2	29.6 ± 4.3	28.5 ± 4.1
< 18.5	0 (0)	0 (0)	0 (0)
18.5-24.9	6 (17.6)	4 (16.7)	2 (20.0)
25.0-29.9	11 (32.4)	7 (29.2)	4 (40.0)
30-0-34.9	16 (47.1)	12 (50)	4 (40.0)
35.0-39.9	1 (2.9)	1(4.2)	0 (0)
> 40.0	0 (0)	0 (0)	0 (0)

* Data reported as means ± SD and frequencies and (percentages).

DM treatment was categorized as: diet and exercise alone, use of oral medication, or use of insulin with or without oral medication. Change in DM treatment category was characterized as worsening (e.g. shifting from a treatment of diet alone to a treatment with oral medication), not changing, or improving (e.g. shifting from the use of insulin to oral medications, only) over four time intervals: admission to discharge, discharge to 3 months, 3 months to 6 months, and 6 months to 12 months post-transplant. Change in

DM treatment category overtime for the study population is illustrated in Figure 5. The most significant change in diabetes treatment occurred between admission and discharge during which 50% of patients required more intense DM treatment. There were some changes in DM treatment regimen from discharge to three months changes in DM treatment regimen occurred after 3 months.

Figure 5. Change in Diabetes Mellitus Treatment Regimen after Kidney Transplantation among Adult Patients with Type 2 Diabetes Mellitus at Admission



Change in DM treatment over time and its relationship to pre-transplant BMI are summarized in Table 7. Average pre-transplant BMI was not significantly different among patients whose DM treatment regimen worsened, remained unchanged, or improved at discharge, 3, 6, and 12 months post-transplant.

Table 7. Change in Diabetes Mellitus Treatment Regimen and Pre-Transplant Body Mass Index of Adult Kidney Transplant Patients with Type 2 Diabetes Mellitus*.

Change in Treatment Regimen	n=34	Body Mass Index (kg/m^2)
Admission to Discharge		
Worsening	17 (50.0%)	29.2 ± 4.7
No change	17 (50.0%)	29.4 ± 3.8
Improvement	0 (0%)	-
Discharge to Three Months		
Worsening	3 (8.8%)	29.4 ± 7.8
No change	30 (88.2%)	29.1 ± 3.9
Improvement	1(2.9%)	34.3
Three to Six Months		
Worsening	0 (0%)	-
No change	33 (97.1%)	29.3 ± 4.3
Improvement	1(2.9%)	30.7
Six to Twelve Months		
Worsening	0 (0%)	-
No change	32 (94.1%)	29.4 ± 4.2
Improvement	2 (5.9%)	27.5 ± 4.6

* Data reported as means ± SD and frequencies and (percentages).

McNemar's test for correlated proportions was used to determine whether change in diabetes treatment during one follow-up time interval influenced the change in DM treatment at the next follow-up time interval (Table 8). There was a strong association between change in DM treatment from admission to discharge and change in DM

treatment from discharge to three months and this was significant (X_3^2=13.25; p-value = 0.001). This finding suggests that, in almost all cases, the time at which a patient's DM treatment regimen changes is from admission to discharge or discharge to three months. Change in DM treatment during, 3 months, 6 months and 12 months and their respective time periods was not significant (X_2^2=3.00; p-value = 0.223 and X_1^2=1.00; p-value = 0.317).

Table 8. Influence of Change in Diabetes Treatment Regimen from One Follow-up Period to the Next Among Adult Kidney Transplant Patients who had Type 2 Diabetes Mellitus at Admission.

Admission to Discharge	Discharge to 3 Months			
	Worsening	No change	Improvement	% of Total (n=34)
Worsening (n=17)	2	15	0	17 (50%)
No Change (n=17)	1	15	1	17 (50%)
Improvement (n=0)	0	0	0	0 (0%)
% of Total (n=34)	3 (8.8%)	30 (88.2%)	1 (2.9%)	
				X_3^2=13.25; p-value = 0.001

Discharge to 3 months	3 Months to 6 Months			
	Worsening	No change	Improvement	% of Total (n=34)
Worsening (n=3)	0	3	0	3 (8.8%)
No Change (n=30)	0	29	1	30 (88.2%)
Improvement (n=1)	0	1	0	1 (2.9%)
% of Total (n=34)	0 (0%)	33 (97.1%)	1 (2.9%)	
				X_2^2=3.00; p-value = 0.223 (NS)

3 Months to 6 Months	6 Months to 12 Months			
	Worsening	No change	Improvement	% of Total (n=34)
Worsening (n=0)	0	0	0	0 (0%)
No Change (n=33)	0	32	1	33 (97.1%)
Improvement (n=1)	0	0	1	1 (2.9%)
% of Total (n=34)	0 (0%)	32 (94.1%)	2 (5.9%)	
				X_1^2=1.00; p-value = 0.317 (NS)

Because of the significance (p-value = 0.001) associated in change in DM treatment from admission to discharge and discharge to three months (Table 8), the impact of change in BMI on change in DM treatment from discharge to 3 months was assessed using Fisher's exact test (Table 9). A change in BMI from admission to 3 months after transplant was correlated with a change in DM treatment regimen from admission to three months, but this correlation was not significant (p-value = 0.6).

Table 9. Correlation between Change in Diabetes Mellitus Treatment Regimen from Discharge to 3 Months among Adult Kidney Transplant Patients with Pre-existing Type 2 Diabetes Mellitus and Change in Body Mass Index (BMI) from Admission to Three Months (n=34)*.

	Change in BMI from Admission to 3 Months	
Change in Diabetes Mellitus Treatment Regimen from Discharge to 3 months	Increase in Body Mass Index	Decrease in Body Mass Index
Worsening (n=3)	1 (5.9%)	2 (11.8%)
No Change (n=30)	16 (94.1%)	14 (82.4%)
Improvement (n=1)	0 (0%)	1 (5.9%)
Total	17	17 p-value = 0.6 (NS)

* Data reported as frequencies and (percentages).

Chapter 5

Discussion

Summary

The results of this study were generated from information abstracted from the Electronic Medical Records of 179 adults patients who had a kidney transplant at OHSU between August 2008 and February 2011. Our goal was to determine if body mass index (BMI) at admission could predict the development of new-onset diabetes mellitus after Transplant (NODAT) or the worsening of pre-existing diabetes mellitus (DM). In addition, we assessed whether the development of NODAT or the worsening of pre-existing DM was predicted by age, ethnicity, type of immunosuppressant medication, etiology of end-stage renal disease (ESRD), or sex.

There were three important conclusions of this study. First, the odds of developing NODAT increased per unit increase in pre-transplant BMI at discharge, 3 months and 6 months after transplant. Second, development of NODAT was most likely to occur by 3 months after transplantation. Third, among patients with pre-existing DM, if their condition worsened, it worsened within three months after transplantation.

These findings are critical because, despite the success of kidney transplantation, complications such as NODAT or the worsening of pre-existing DM still occur and appear to contribute to increased mortality and increased incidence of cardiovascular disease post-transplant [34]. In a study conducted at OHSU and published in 2006, de Mattos, et al., identified obesity (adjusted hazard ratio 2.92; p-value < 0.001), diabetes (adjusted hazard ratio 2.63; p-value < 0.001), and overweight status (adjusted hazard ratio 1.68; p-value = 0.04), as risk factors that contributed to cardiovascular events following kidney transplantation[35]. In 2007, Joss, et al., reported that the ten-year patient survival

rate was lower in patients who had pre-existing DM (65.3%) or who developed NODAT (67.1%) compared to patients without DM (81.9%)[25].

Body Mass Index and the Development of New-Onset Diabetes Mellitus After Transplant

Of the 134 patients in our sample who did not have DM prior to transplant, 14.2% were diagnosed with NODAT by discharge. The cumulative incidence of NODAT at 3, 6, and 12 months after kidney transplant was 19.4%, 20.1%, and 19.4%, respectively. Our findings are similar to previously published results by Razeghi, et al., who reported that 33% of their patients developed NODAT by 6 months of transplantation, and Joss et al., who reported 7.7% of their patients developed NODAT within 12 months of transplatation[3, 25]. In 2003, the development of NODAT reported by Kasiske, et al., using the USRDS database, was 9.1% and 24% at 3 and 12 months respectively[27]. Although our current study's report of the cumulative incidence of NODAT within one year of transplant was similar to previously published reports, the percentage of patients diagnosed by discharge and 3 months was higher.

In our study, 73.6% of the patients who developed NODAT were diagnosed by discharge and nearly 100% were diagnosed by 3 months post transplant. Our results are slightly higher than previously published literature where Bayes, et al., reported that 77.3 % of those who developed NODAT were diagnosed within 3 months and Parikh, et al., reported that 72% of the patients who developed NODAT were diagnosed within 2 months after kidney transplantation[24, 28]. These differences in rates of NODAT development could be due to lack of uniform criteria for diagnosis of NODAT,

differences in follow-up periods, differences among racial and ethnic distributions, or changes in immunosuppressant regimens [36].

The primary hypothesis of this study, that patients who are obese at the time of kidney transplantation are more likely to develop NODAT than patients who are not obese, was not able to be tested due to the small sample of obese patients and the insufficient power for this analysis. Because of the small variance in BMI among the subgroup who developed NODAT the primary hypothesis was adjusted to test the hypothesis that pre-transplant BMI (as a continuous variable instead of as a categorical variable) was associated with the development of NODAT or the worsening of pre-existing DM. Our study demonstrates that the odds of developing NODAT at discharge, 3, and 6 month is higher for each unit increase for pre-transplant BMI for both males and femals. We found that, when controlling for other variables, the odds of developing NODAT by discharge, 3, or 6 months after transplantation were 1.11 (CI 1.0-1.23), 1.13 (CI 1.03-1.24), and 1.15 (CI 1.05-1.27) per unit increase in pre-transplant BMI, respectively. These findings were slightly lower than the previously published report by Parikh, et al., who demonstrated that a one unit increase in pre-transplant BMI increased the odds of developing NODAT by 1.22 (CI 1.04-1.42) in the first 6 months after transplantation [28]. The differences in our results may be due in part to the differences in sample sizes, 54 versus 134.

Our study also analyzed pre-transplant BMI and the odds of developing of NODAT 12 months after kidney transplantation. The odds of developing NODAT at 12 months were different for males and females. After adjusting for sex, we concluded that the odds of developing NODAT by 12 months increased per unit increase in pre-

transplant BMI by 1.34 (CI: 1.12-1.61; p-value = 0.002) for males and 1.10 (CI: 0.97-1.24; p-value = 0.144) for females, although this relationship was not significant for females. These findings suggest that males are at an elevated risk for developing NODAT at 12 months post-transplant because they tend to have higher pre-transplant BMIs, a risk factor that could be modified.

Body Mass Index and Change in Treatment of Pre-existing Diabetes Mellitus in Adult Kidney Transplant Patients within 12 Months of Transplantation.

The secondary hypothesis of this study was to test that worsening of pre-existing DM after transplant was higher among patients who were obese at the time of transplant than those who were not obese at the time compare to transplant. We were not able to test this hypothesis due to small sample size and insufficient power. We did, however, determine that if a patient's DM treatment changed after kidney transplantation, changes were most likely to occur between admission and discharge or discharge and three months.

Strengths

The major strength of this study is that 204 medical records were reviewed and most patients 179, (87.7%), met the inclusion criteria. The review consisted of patients who received a kidney transplant between August 2008 and February 2011, which was a relatively short period of time and allowed for consistency in surgical and treatment procedures. Multiple variables such as pre-transplant BMI, sex, eGFR, plasma creatinine concentration, age, length of stay, and the development of NODAT or changes in pre-

existing DM treatment were all assessed. The development of NODAT and changes in DM treatment were also assessed at multiple time points.

Limitations

One limitation is that this was a preliminary study and the number of patients included in the analysis was set, a priori, at 200. This arbitrary number did not result in a large enough number of patients who had BMIs in the Class I, Class II, or Class III category of obesity. We were unable to determine whether patients who are obese at the time of transplant are more likely to develop NODAT. Specific BMI categories could not be assessed to determine if there was a clear BMI cut-off point above which development of NODAT was more likely. Instead BMI was analyzed as a continuous variable in logistic regression models to determine the odds of developing NODAT at discharge, 3, 6, and 12 months. A pre-screen of kidney transplant patients to identify those with higher BMIs could have been preformed to increase the number of patients within the higher BMIs.

An additional limitation was the small variance in BMIs of the subgroup of transplant patients who had pre-existing DM. This lack of variance in BMIs limited our ability to determine if BMI was associated with the worsening of pre-existing DM. Kidney transplant patients with pre-existing DM could have been pre-selected and then analyzed using a case control model. Including a larger number of patients with pre-existing DM would allow statistical analysis with sufficient power to detect whether BMI was associated with changes in DM treatment.

Future Direction

Our study indicated that the early months after a kidney transplant are when NODAT is likely to develop and when worsening of pre-existing DM occurs. Therefore, patients at risk for developing NODAT or patients with pre-existing DM should be monitored and evaluated for changes in BMI and dietary intake by the multi-disciplinary transplant team, including dietitians.

To our knowledge whether patients with pre-existing DM and higher BMIs at admission are more likely to experience worsening of their DM has not been addressed by other investigators. Although the results of this study were inconclusive, this novel question merits further study.

Conclusions

Based on the results reported here, we conclude that the odds of developing NODAT at discharge, 3 & 6 months increased significantly per unit increase in of pre-transplant BMI. Therefore, BMI is an independent risk factor for the development of NODAT, which is consistent with the findings of other research[28]. This study also concluded that if NODAT developed, it developed by 3 months after kidney transplantation.

The results of this study found that pre-existing DM treatment worsened by 3 months post-transplantation in half of the patients. We were unable to determine if the worsening of DM treatment was associated with pre-transplant BMI, although we did conclude that it was not associated with changes in BMI after transplant.

This work suggests that early post-transplant interventions to prevent weight gain may reduce the development of NODAT and increase patients survival as well as the quality of life after transplantation[34, 35]. We show that the first three months after kidney transplantation are particularly critical for both the development of NODAT and changes in DM status.

Appendix 1 – Evidence Table Summarizing Association of BMI and New on Set Diabetes or the Worsening of Pre-Existing Diabetes in Kidney Transplant Patients

Citation	Study Design	Subjects/ Characteristics	Outcomes
Razeghi E, Heydarian P, Amerian M, Pourmand G. The risk factors for diabetes mellitus after kidney transplantation. *Saudi J Kidney Dis Transpl*. 2010;21(6):1038-1043.	Prospective study of kidney transplant patients receiving their first transplant. Saudi Arabia	N=109 Duration: 6/03-5/04 Pt were excluded if they had diabetes at the time of transplant. Followed for 6 month post-transplant to see if they developed NODAT.	30 patients (33%) of the 90 (82.5%) that completed the study, developed NODAT Patients were at an increased risk of developing NODAT if they were: • > 50 y.o. (OR 3.2) • elevated dose of prednisolone (≥15mg/day) (OR 12.1) • elevated dose of cyclosporine (≥ 240 mg/day) (OR 40.1) • ESRD due to polycystic kidney disease (OR 11.8) Patients were at a decreased risk of developing NODAT if they were: • ESRD due to glomeral nephritis (OR 1.4)
Johnston O, Rose CL, Webster AC, Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *Journal of the American Society of Nephrology*. 2008;19(7):1411-1418.	Prospective study of the association between sirolimus use at the time of transplantation and NODAT. Canada	20,124 adult patients who received their first kidney transplant and did not have ESRD due to diabetes at the time of transplant were studied. Participants were followed on average of 2.93 years post-transplant.	Sirolimus –treated patients were at increased risk for NODAT, when used independently or in combination with cyclosporine (adjusted hazard ratio 1.61), tacrolimus (1.66), or an antimetabolite (1.36) in comparison to patients who were not prescribed sirolimus.
Shehab-Eldin W, Shoker A. Predictors of new onset of diabetes after transplantation in stable renal recipients. *Nephron*. 2008;110(1):1-9.	Cross-sectional prospective study of renal transplant patients to identify potential risk factors of development of NODAT. Canada	55 patients were followed for 14.98 ± 3.97 months. The groups were divided among the following criteria: Group A , n= 34 with who had normoglycemia Group B, n= 21 patients with impaired fasting glucoses, prior to kidney transplant. Testing Insulin, pro-insulin, adiponectin,	11.8 and 19% of groups A and B, respectively, developed NODAT. A baseline fasting insulin level of 54.54 mU/I predicted the development of NODAT with a specificity of 95.45% and was the only significant factor in the multivariate analysis.

		insulin resistance, and beta-cell function were calculated and correlated, with development of NODAT.	
Bayes B, Granada ML, Pastor MC, et al. Obesity, adiponectin and inflammation as predictors of new-onset diabetes mellitus after kidney transplantation. *American Journal of Transplantation*. 2007;7(2):416-422	Prospective analysis from 1994-2004. Objective was to see if there was a correlation between adiponectin and NODAT. Spain	199 non-diabetic patients (128 men; age: 53 ± 11 years; body mass index (BMI) 24.98 ± 3.76 kg/m^2) were included. Pre-transplant plasma glucose, insulin, adiponectin, CRP, IL-6 and PAPP-A were measured. The patients were then tested at 3 month post transplant.	45 patients (22.6%) developed NODAT and 77.3 % of those diagnosed were diagnosed within 3 months post-transplant. Patients who developed NODAT had a greater pre-transplant BMI 26.59 ± 4.27 vs patients who did not develop NODAT 24.51 ± 3.46 ($p = 0.005$). Adiponectin was lower 11.25 ± 5.04 vs 16.32 ± 6.52 ($p < 0.001$). CRP was higher 6.11 vs 3.4 ($p = 0.032$) in patients with NODAT. Multivariate logistic regression and Cox analysis showed that the calcineurin inhibitor used, pre-transplant BMI and pre-tranplant adiponectin were predictors of NODAT. ROC analysis showed that an adiponectin concentration of 11.4 mg/L had a significant negative prediction for NODAT risk. Of the inflammatory markers studied, adiponectin proved to be an independent predictor of NODAT.
Hur KY, Kim MS, Kim YS, et al. Risk factors associated with the onset and progression of post-transplantation diabetes in renal allograft recipients. *Diabetes Care*. 2007;30(3):609-615.	Prospective study to analyze the incidence of NODAT and investigate the factors contributing to the incidence of NODAT. Korea	N=77 patients were given a glucose tolerance test one week prior to transplant and 1 year and 7 years after transplantation.	N= 38 (23.3%) never developed NODAT within the seven years. N=12 (15.5%) developed NODAT at 1 year then recovered by 7 years. N=9 (11.6%) developed NODAT at 7 years but did not have diabetes at one year. N=18 (49.3%) developed diabetes at 1 year and still had diabetes at 7 years.

			Older age (≥ 40 years of age) was a higher predictor (49.3%) for NODAT at one year and elevated BMI (25kg/m^2) was a predictor of NODAT common at year seven.
Joss N, Staatz CE, Thomson AH, Jardine AG. Predictors of new onset diabetes after renal transplantation. *Clin Transplant*. 2007;21(1):136-143.	Retrospective review of renal transplants performed between 1994 and 2004 at a single center. UK	N=787 NODAT was diagnosed in patients who had two random plasma glucose concentrations >11.1 mmol/L (200 mg/dL) after the first month post-transplant or patients who required treatment for hyperglycaemia within the first month and continued treatment thereafter.	Risk factors for the development of NODAT were older age, heavier weight at time of transplantation, higher mean pre-transplant random plasma glucose concentrations, higher plasma glucose within the first seven days post-transplant and use of tacrolimus. The incidence of NODAT was 7.7%. The incidence of NODAT requiring either insulin or oral hypoglycaemic agents was 4.5%. Ten year patient survival was 67.1% in patients with NODAT compared with 81.9% for those without diabetes and 65.3% in patients known to have diabetes pre-transplant. There were no differences in graft survival.
Schiel R, Heinrich S, Steiner T, Ott U, Stein G. Post-transplant diabetes mellitus: Risk factors, frequency of transplant rejections, and long-term prognosis. *Clinical & Experimental Nephrology*. 2005;9(2):164-169.	Consecutive patients with ESRD, but without DM who received kidney transplantation at a single center beginning in 1992. US	N = 253 Age: 52.2 ± 12.6 years Body mass index: 22.0 ± 7.9kg/m^2 Follow up was 3.3 ± 1.6 years (range, 0.1–17.7) years	In total, 43patients (17%) developed NODAT after transplantation. Patients with NODAT were significantly older(50.3 ± 11.4 vs 50.9 ± 12.5 years) and had a higher BMI (24.0 ± 8.5 vs 21.6 ± 7.8kg/m2; *P* = 0.077). There was no differences between the groups with respect to blood pressure control or the frequency and dosage of immunosuppressive drugs such as cyclosporine, tacrolimus, and sirolimus during the follow up.
Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the united states.	Observational studies and clinical trials. Using data from the United Renal Data System who were Medicare beneficiaries who received their first kidney transplant in 1996–2000 US	N = 11,659 Patients who received their first kidney transplant were followed	The cumulative incidence of NODAT was 9.1%, 16.0%, and 24.0%, at 3, 12, and 36 months post-transplant, respectively. Using Cox's proportional hazards analysis, risk factors for NODAT included age, African American race, Hispanic ethnicity, male

American Journal of Transplantation. 2003;3(2):178-185.			donor, increasing HLA mismatches, hepatitis C infection, body mass index ≥30 kg/m^2 , and the use of tacrolimus as the initial maintenance immunosuppressive medication.
Parikh CR, Klem P, Wong C, Yalavarthy R, Chan L. Obesity as an independent predictor of post-transplant diabetes mellitus. *Transplant Proc*. 2003;35(8):2922-2926.	Retrospective analysis of medical records of renal allograft recipients, The patients who received a kidney transplant from January 1998 to March 2001 were screened to identify the cases of NODAT. US	A total of 18 cases and 36 controls were identified. Controls were matched for immunosuppressive regimen, gender, and type of donor.	The incidence of NODAT was 10%. Of these cases, 72% developed NODAT within the first 2 months after transplant, and 38% of them required insulin. BMI was significantly associated with PTDM (adjusted odds ratio 1.22) while controlling for number of rejections, age, and other factors. Obesity was an independent predictor of NODAT.
Miles AM, Sumrani N, Horowitz R, et al. Diabetes mellitus after renal transplantation: As deleterious as non-transplant-associated diabetes? *Transplantation*. 1998;65(3):380-384	Prospective study of the effects of post-transplant diabetes on long-term 9.5±1.3 year, graft survival and patient survival in the 11.8% of the 40 patients renal transplant population who developed NODAT compared to match paired who did not develop NODAT US	n= 78 n=40 developed NODAT n=38 patients without NODAT	48% graft survival in NODAT and 70% graft survival in controls after 12 years. NODAT was a significant predictor of graft loss independent of age, sex, and race.

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