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I, Amy Colleen Wilson, hereby submit this as part of the requirements for the degree of:

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It is entitled:

High Prevalence of the Metabolic Syndrome and Associated Left Ventricular Hypertrophy in Pediatric Renal Transplant

Recipients

Approved by:

Paul A. Succop, Ph.D.
John J. Bissler, M.D.
James E. Heubi, M.D.
Mark M. Mitsnefes, M.D., M.S.
Title: High Prevalence of the Metabolic Syndrome and Associated Left Ventricular Hypertrophy in Pediatric Renal Transplant Recipients

Name: Amy C. Wilson

Date: May 27, 2008

Previous degrees: B.S., M.D.

Degree to be conferred: M.S.

Department: Environmental Health

College: Medicine

Committee Chair: Paul A. Succop, Ph.D.
ABSTRACT

Background: Individual cardiovascular (CV) risks are common after pediatric renal transplant. The prevalence of metabolic syndrome and its association with CV abnormalities are unknown in this population.

Methods and Results: Multi-center retrospective review was performed at time of and at 1-year post transplant for 256 consecutive patients. 37.6% met diagnostic criteria for metabolic syndrome at 1-year post transplant. Among 181 patients with complete data at both time points, 18.8% met diagnostic criteria at time of transplant, versus 37.0% at 1-year (p<0.0001). Among patients with metabolic syndrome, mean LV mass index (LVMI) was 48.3g/m².7 versus 40.0g/m².7 (p=0.0008) in those without. Left ventricular hypertrophy (LVH) was more common in those with metabolic syndrome (55% versus 32%) (OR 2.6, 95% CI 1.2-5.9).

Conclusions: Metabolic syndrome is common at time of pediatric renal transplant, and prevalence rises sharply at 1-year post transplant. Metabolic syndrome is associated with increased LVMI and LVH in this population.
Acknowledgements

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Figure 4: Distribution of LVMI (gm/m³.7) by metabolic syndrome status.

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INTRODUCTION

Over the last few decades renal transplantation has evolved as the treatment of choice for children with end-stage renal disease (ESRD). As a result of the progress made in pre- and post-transplantation care, children with ESRD now routinely survive to adulthood. Unfortunately, despite these successes, the life expectancy for these patients remains low, with much of their excess mortality due specifically to premature cardiovascular disease (CVD) (1-4). In fact, CVD is the most common cause of death in young adults who developed ESRD during childhood (2-4). The metabolic syndrome, a constellation of interrelated cardiovascular risk factors, is a significant risk factor for developing CVD (5). It is very common (~69%) in adults on maintenance dialysis, most likely due to high prevalence of type II diabetes (6). In contrast to adults, diabetes is a rare cause of ESRD in children. Nevertheless, children after transplantation have a high prevalence of traditional CVD risk factors. For example, the prevalence of obesity at time of transplantation is 12%; however, it reaches 29% at 1 year after transplantation (7). Approximately 70% of transplant recipients are taking antihypertensive medications at one year post-transplant (8). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines indicate that 40-60% of children have dyslipidemia after transplant (9). Recent studies also indicate that insulin resistance is a frequent finding in children at the time of transplant (10-14). While studies have evaluated individual components of the metabolic syndrome, no study has defined the prevalence of the metabolic syndrome in children after transplantation or evaluated the association between the metabolic syndrome and CVD in this high-risk population.
METHODS

A retrospective review of consecutive pediatric renal transplant recipients was carried out at 6 centers (via collaboration through the Midwest Pediatric Nephrology Consortium). All patients were transplanted between January 2000 and December 2006. The study was reviewed and approved by the Institutional Review Boards of all participating centers.

Inclusion criteria were as follows: functioning renal transplant at 1-year post transplant and age <21 years at time of transplant. The exclusion criteria were diabetes mellitus (type I or II) preceding transplant and lack of follow-up through one year post-transplant at the participating centers. Charts were reviewed for demographic (age, gender, race), clinical (etiology of ESRD, medications, history of prior transplants, history of dialysis prior to transplant), anthropometric (height, weight, blood pressure), and laboratory data (serum glucose, total cholesterol, HDL-C, LDL-C, triglycerides, creatinine) at time of and at 1-year post-transplant. All anthropometric measurements were performed using methods that were standard of care at each institution. Laboratories were measured in the clinical laboratories of the respective institutions using standard techniques. For time of transplant evaluation, serum was collected from live donor recipients on the morning of surgery after an overnight fast. For patients who received cadaveric transplants the fasting status could not be accurately determined from the records. One-year post transplant evaluations at participating centers routinely include determination of fasting glucose and lipid profiles. Medication information collected specifically included all immunosuppressive agents (along with dosage and, where applicable, drug levels), antihypertensive agents, and lipid modifying therapies. Cumulative corticosteroid dose for the entire post-transplant year was calculated in addition to recording the daily dosage at the 1-year post transplant evaluation.
The metabolic syndrome was defined by meeting any three of the following five criteria:
1) body mass index (kg/m²) >97th percentile for age and gender, or >25kg/m², whichever is lower, 2) hypertension (systolic or diastolic blood pressure >95th percentile for age, gender, and height, or on antihypertensive medication), 3) high density lipoprotein (HDL-C) <5th percentile for age and gender (or on lipid-modifying therapy), 4) triglycerides >95th percentile for age and gender (or on lipid-modifying therapy), 5) fasting glucose >100mg/dL or requirement for insulin or oral hypoglycemic therapy. Patients were classified as to the presence or absence of the metabolic syndrome both at time of transplant and at 1-year post transplant.

Echocardiographic data were collected only at the four centers at which routine echocardiography is performed at 1-year post transplant. The following information was abstracted from the records: left ventricular internal dimension (LVID) in end diastole, interventricular septal thickness (IVST) in end diastole, posterior wall thickness (PWT) in end diastole. Left ventricular mass (LVM) was calculated according to the recommendations of the American Society of Echocardiography: 

\[ LVM = 0.8[1.04([LVID+PWT+IVST]^3 - [LVID]^3)] + 0.6gm \] (15). Left ventricular mass indexing (LVMI) was used in order to normalize LVM to body size independent of the presence of obesity, and was calculated as LVM (g) divided by height^{2.7} (m^{2.7}). Left ventricular hypertrophy was defined as LVMI >95th percentile for age and gender (16, 17). LV geometry was further evaluated based on both LVMI and relative wall thickness (RWT) (18). RWT was calculated as (PWT + IVST)/ LVID, with normal being defined as RWT <0.41. Normal geometry was defined as LVMI <95th percentile and RWT <0.41; concentric remodeling was defined as LVMI <95th percentile with RWT >0.41; eccentric LVH was defined as LVMI >95th percentile with RWT <0.41; concentric hypertrophy was defined as LVMI>95th percentile with RWT >0.41 (19).
Data management and statistical analysis: All data collected was stored in password protected Excel databases. Analyses were performed using SAS 9.1® statistical software (SAS Institute, Cary, NC). McNemar’s test for paired samples was used to compare the prevalence of the metabolic syndrome at time of and at 1-year post transplant. Two sample t-tests were used to compare means ± SD of continuous variables. Categorical variables were compared using chi-squared or Fisher’s exact test, as appropriate. The Bonferroni correction for multiple comparisons was applied where appropriate. Backward elimination multivariable logistic regression analysis was used to determine the presence of independent predictors of the metabolic syndrome, beginning with inclusion of age, race, gender, etiology of ESRD, and any factors which were found to be associated (p<0.1) with metabolic syndrome in univariate analysis. Linear regression analysis was used to evaluate the association between LVMI and metabolic syndrome after adjustment for other factors identified in univariate analysis to be significantly associated with increased LVMI. Patients were excluded from analyses in any case in which missing data had the potential to change the individual’s categorization as having the metabolic syndrome or not.

RESULTS

Patient Characteristics

A total of 306 patients from 6 centers were transplanted during the study period. A total of 256 met inclusion criteria (see Figure 1). Adequate data for categorization with respect to the metabolic syndrome at 1-year post transplant was available for 234 (91%); 181 records (71%) contained adequate data for categorization both at time of and at 1-year post transplant; 113 patients (44%) from 4 centers had both a routine echocardiogram and adequate data for diagnosis
of metabolic syndrome at 1-year post transplant. Demographic and clinical characteristics were similar across all subsets and are summarized in Table 1. At 1-year post transplant, 175 of 234 patients (75%) were on triple immunosuppression: among these patients, 114 were treated with corticosteroids, calcineurin inhibitors (CNI, either cyclosporine or tacrolimus), and mycophenolate mofetil (MMF); 32 were on corticosteroids, sirolimus, and MMF; the remaining 28 were on other corticosteroid-based combinations. Fifty-two (22%) patients were on two-drug regimens; among them, 38 patients were treated with corticosteroid-sparing immunosuppression regimens. Six patients were on four-drug regimens which included sirolimus, CNI, MMF, and corticosteroids. One patient was on single-immunosuppression with prednisone. Detailed information on specific regimens is available in Table 2.

Prevalence of Metabolic Syndrome

The prevalence of the metabolic syndrome at 1-year post transplant was determined based on the 234 patients for whom diagnostic information was available: 88 patients (37.6%, 95% CI 31.4-44.2%) met criteria for diagnosis of the metabolic syndrome. Among 99 non-lean patients (BMI >25kg/m² or BMI > 85th percentile at one year post transplant), 56 (56.6%, 95% CI 46.2 -66.5%) had metabolic syndrome. Specifically, among 41 patients with obesity (BMI > 97th percentile at one year), 33 (80.5%, 95% CI 65.1-91.2%) had metabolic syndrome. In univariate analysis, pre-transplant BMI > 85th percentile, steroid-sparing immunosuppression, glomerular disease as etiology of ESRD, older age, and lower graft function were found to be significantly associated with the metabolic syndrome (all p<0.05). Multivariable logistic regression models including gender, race, and factors identified in univariate analysis were constructed. Only increasing age, glomerular disease, and pre-transplant BMI > 85th percentile retained statistically significant association with the metabolic syndrome in the model (details in
Cumulative corticosteroid dose, CNI exposure, and sirolimus exposure were all assessed and were not found to have a significant association with the metabolic syndrome.

Among patients with complete data at time of and 1-year post transplant (n=181), the prevalence of metabolic syndrome at time of transplant was 18.8% (95% CI 13.4-25.3%) compared to 37.0% (95% CI 30.0-44.5%) at 1-year post transplant (p<0.0001). The frequency of each individual criterion for the metabolic syndrome at time of and 1-year post transplant is displayed in Figure 2: hyperglycemia, overweight/obesity, and hypertension demonstrated significant changes in prevalence between the two time points. There were 8 patients who met criteria for diagnosis of the metabolic syndrome who no longer met criteria by one year post-transplant. These patients tended to be younger (although the difference did not reach statistical significance), and were lighter, with significantly lower absolute BMI and BMI Z scores at both time points, than those patients who met diagnostic criteria at both time points.

**Incidence of Metabolic Syndrome**

Among a cohort of 147 patients without the metabolic syndrome at time of transplant, 41 patients (27.9%, 95% CI 20.8-35.9%) had developed the metabolic syndrome at their 1-year post transplant evaluation. Significant factors associated with incident metabolic syndrome identified in a univariate analysis included pre transplant BMI >85th percentile and corticosteroid-sparing immunosuppression. Cumulative corticosteroid dose, CNI exposures, and sirolimus exposure were not associated with the metabolic syndrome. Patients who developed the metabolic syndrome had mean change in BMI of +4.0kg/m² compared to +1.8kg/m² for those without (p=0.0002). Changes in BMI Z-scores were also analyzed: those who developed the metabolic syndrome had mean change in BMI Z-score +1.39 compared to +0.42 (p=0.13) in those who did not develop the metabolic syndrome. Among non-lean patients (BMI >25kg/m² or BMI >85th
percentile at 1-year post transplant) who did not have the metabolic syndrome at transplant (n=49), the incidence of the metabolic syndrome was 41.2% (95% CI 27.6-55.8%). Among lean patients (BMI <25kg/m² and BMI <85th percentile at 1-year post transplant, n=96), the incidence of the metabolic syndrome was 20.8% (95% CI 13.2-30.2%, p=0.009 compared to non-lean patients). Frequencies of individual criteria for metabolic syndrome among lean and non-lean patients are displayed in Figure 3. Multivariable logistic regression models of incident metabolic syndrome included age, gender, race, and all factors identified in univariate analysis to have p<0.1. Only glomerular disease as etiology of ESRD was significantly associated with development of the metabolic syndrome (OR 2.83, 95%CI 1.10-7.29).

**Metabolic Syndrome and Left Ventricular Hypertrophy**

One-hundred thirteen patients from 4 centers had routine echocardiogram in addition to complete laboratory evaluation at 1-year post transplant. Among 38 patients with metabolic syndrome, mean LVMI was 48.3g/m²; among 75 patients without metabolic syndrome, it was 40.0g/m² (p=0.0008), Figure 4. In addition to metabolic syndrome, systolic blood pressure (p=0.002), age (p=0.0008), and BMI percentile (p=0.0008) were each significantly correlated with LVMI in univariate analysis. In order to investigate whether the effect of metabolic syndrome on LVMI was independent of higher blood pressures and/or BMI in this group, multivariable linear regression analysis was performed. After simultaneous adjustment for all of the above factors, only age in years (β=-1.0, p<0.0001), and the presence of metabolic syndrome (β=8.5, p=0.0004) were significantly associated with increased LVMI. Twenty-one patients (55.3%) with metabolic syndrome had LVH compared to 24 patients (32%) without metabolic syndrome (OR 2.6, 95% CI 1.2-5.9). Distribution of LV geometry in the two groups is
demonstrated in Figure 5. Eccentric hypertrophy was significantly more prevalent in the metabolic syndrome group (34% versus 15%, OR 3.0, 95% CI 1.2-7.6).

**DISCUSSION**

This analysis demonstrates that nearly 40% of pediatric renal transplant patients meet criteria for diagnosis of the metabolic syndrome at one year after renal transplantation. More significantly, a substantial number (28%) of these young patients have developed metabolic syndrome during the first post transplant year. While disturbing, the high prevalence and incidence of metabolic syndrome in this population are not surprising when taken in the context of prior studies demonstrating high prevalence of individual traditional CVD risk factors (hypertension, dyslipidemia, insulin resistance, and overweight/obesity) in this population (7-14). In the current study we were unable to fully assess the prevalence of insulin resistance, instead relying on fasting glucose as a surrogate measure. However, previous studies in pediatric patients with CKD including renal transplant recipients have demonstrated much higher prevalence of insulin resistance than prevalence of fasting hyperglycemia (20, 21). Thus, our study is more likely to underestimate than overestimate true disease prevalence and incidence following pediatric renal transplant.

The results of the current study suggest that higher pre transplant BMI percentile confers higher risk for the metabolic syndrome, with nearly 60% of patients whose pre-transplant BMI exceeded the 85th percentile meeting diagnostic criteria at one year post transplant. This rate is comparable to those reported for populations of obese children in other studies (22-24). However, it should be noted that those studies examined rates of metabolic syndrome in patients with BMI > 97th percentile. To be consistent with this literature, we did examine the group of
patients whose BMI at one year exceeded the 97th percentile. In this group, the prevalence of the metabolic syndrome at one year was 80%, the highest reported for any pediatric population. This illustrates the excess risk for the metabolic syndrome that overweight and obese renal transplant recipients experience compared to obese children without renal disease. In addition, the finding that 20% of children who were lean at both time of and 1-year post transplant in this cohort developed the metabolic syndrome in the year after transplant is in striking contrast to healthy lean children, in whom the metabolic syndrome is virtually nonexistent. The etiology of the metabolic syndrome in these patients is likely multi-factorial, with contributions from underlying renal disease, side effects of immunosuppressive medications, and low levels of physical activity all playing a role (25).

A problem common to all pediatric studies is that there are no clearly defined standard criteria for the metabolic syndrome in children. Furthermore, studies have documented substantial variations in pediatric rates of metabolic syndrome depending on which of these classification schemes are used (26). After review of the multiple classification systems, we chose to use a modified version of the criteria used by Weiss et al (20). One modification of the Weiss criteria that we made relates specifically to those patients older than 18 years, for whom the threshold values from the International Diabetes Foundation and the Adult Treatment Panel III (ATP III) guidelines were used (27). The other modification of the Weiss criteria that we made relates specifically to serum glucose level. Weiss et al used fasting serum glucose >110mg/dL as the threshold for hyperglycemia; we have instead used 100mg/dL for two reasons. First, multiple adult metabolic syndrome guidelines, including the most recent from the IDF, utilize a fasting glucose of 100mg/dL. Second, a fasting glucose of 110mg/dL is a relatively insensitive marker of insulin resistance in children with CKD (20). One limitation of this study
concerns the question of whether labs performed at time of transplant were in fact fasting labs. This is particularly of concern in the case of patients who received cadaveric transplants. However, no difference in the prevalence of hyperglycemia or dyslipidemia at time of transplant was seen in patients who had live donor versus cadaveric donor transplants (data not shown).

Although corticosteroids are known to be associated with many of the components of the metabolic syndrome, we did not find any association between the use of corticosteroids and increased rates of metabolic syndrome, or between higher cumulative corticosteroid dose and the metabolic syndrome. In fact, patients who were on corticosteroid-sparing immunosuppression regimens were (in univariate analysis) significantly more likely to develop the metabolic syndrome in the first year post transplant, although the association was not persistent after adjustment for other factors. This suggests that the effect seen in a univariate analysis was likely an artifact of selection bias: patients who were perceived (prior to transplant) as being at higher risk for metabolic complications of corticosteroids were more likely to be placed on steroid-sparing regimens. It should also be noted that children on corticosteroid-sparing regimens continued using other immunosuppressive medications including CNI and/or sirolimus, all of which are known to increase CV risk. In the current study we did not find any significant association between the metabolic syndrome and any individual medication.

We found a strong association between the metabolic syndrome and increased LVMI and higher prevalence of LVH in our cohort. The effect of metabolic syndrome on LVMI persisted even after adjustment for systolic blood pressure and BMI. This is consistent with other studies of left ventricular changes in pediatric renal transplant recipients, which have demonstrated that traditional single CVD risk factors do not explain the burden of increased LVMI and LVH seen in these patients (28-30). As this study was limited to evaluation at one
year after transplantation, we are unable to draw conclusions regarding the long-term cardiovascular complications of the metabolic syndrome in this high-risk population. However, our findings suggest that the constellation of cardiovascular risk factors, rather than any single risk factor, is likely to be an important predictor of future cardiovascular events. Our findings clearly indicate a need for formal, prospective evaluation of the metabolic syndrome and its impact on cardiovascular outcomes in young adult survivors of pediatric ESRD. Most importantly, they indicate that all pediatric renal transplant recipients, not only those who are overweight or obese, should be considered to be at high risk for the metabolic syndrome and treated as such.
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to insulin resistance of the adult treatment panel III diagnostic criteria for identification of
ventricular abnormalities in children, adolescents and young adults with renal disease.
ventricular hypertrophy, treadmill tests, and 24-hours blood pressure in pediatric renal
Table 1: Patient characteristics at 1-year post transplant

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort</th>
<th>Subset for Pre vs Post Transplant Analysis</th>
<th>Subset for Echo Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>234</td>
<td>181</td>
<td>112</td>
</tr>
<tr>
<td>Mean age at transplant, months (SD)</td>
<td>146 (62)</td>
<td>149 (62)</td>
<td>144 (58)</td>
</tr>
<tr>
<td>Timing of evaluation*, months (SD)</td>
<td>12.7 (1.5)</td>
<td>12.7 (1.6)</td>
<td>12.5 (1.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>135 (57.7%)</td>
<td>103 (56.9%)</td>
<td>69 (61.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>99 (42.3%)</td>
<td>78 (43.1%)</td>
<td>44 (38.9%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>147 (62.8%)</td>
<td>110 (60.8%)</td>
<td>83 (73.5%)</td>
</tr>
<tr>
<td>Black</td>
<td>65 (27.8%)</td>
<td>53 (29.3%)</td>
<td>21 (18.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (9.4%)</td>
<td>18 (9.9%)</td>
<td>9 (7.9%)</td>
</tr>
<tr>
<td>Live donor transplant</td>
<td>143 (61.1%)</td>
<td>109 (60.2%)</td>
<td>84 (74.3%)**</td>
</tr>
<tr>
<td>Preemptive transplant</td>
<td>69 (29.5%)</td>
<td>55 (30.4%)</td>
<td>31 (27.4%)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>72 (30.8%)</td>
<td>54 (29.8%)</td>
<td>31 (27.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>162 (69.2%)</td>
<td>127 (70.2%)</td>
<td>82 (72.6%)</td>
</tr>
<tr>
<td>Mean eGFR***, ml/min/1.73m² (SD)</td>
<td>83.7 (28.3)</td>
<td>84.2 (27.6)</td>
<td>74.4 (24.5)</td>
</tr>
</tbody>
</table>

*Refers to number of months between date of transplant and date of post-transplant evaluation.  
**P < 0.05 compared to entire cohort.  ***eGFR, estimated glomerular filtration rate.
Table 2: Immunosuppression regimens of all patients included in analysis of prevalence, organized by number of drugs in regimen.

<table>
<thead>
<tr>
<th>Immunosuppression</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>4-drug regimens</td>
<td>6</td>
</tr>
<tr>
<td>CNI/SRL/MMF/pred</td>
<td>6</td>
</tr>
<tr>
<td>3-drug regimens</td>
<td>175</td>
</tr>
<tr>
<td>CNI/MMF/pred</td>
<td>114</td>
</tr>
<tr>
<td>SRL/MMF/pred</td>
<td>32</td>
</tr>
<tr>
<td>CNI/SRL/pred</td>
<td>17</td>
</tr>
<tr>
<td>CNI/AZA/pred</td>
<td>10</td>
</tr>
<tr>
<td>SRL/AZA/pred</td>
<td>2</td>
</tr>
<tr>
<td>2-drug regimens</td>
<td>52</td>
</tr>
<tr>
<td>SRL/CNI</td>
<td>22</td>
</tr>
<tr>
<td>CNI/MMF</td>
<td>12</td>
</tr>
<tr>
<td>CNI/pred</td>
<td>8</td>
</tr>
<tr>
<td>SRL/MMF</td>
<td>4</td>
</tr>
<tr>
<td>SRL/pred</td>
<td>4</td>
</tr>
<tr>
<td>MMF/pred</td>
<td>2</td>
</tr>
<tr>
<td>1-drug regimens</td>
<td>1</td>
</tr>
<tr>
<td>Pred alone</td>
<td>1</td>
</tr>
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Table 3 Multivariable logistic regression analysis* of factors associated with prevalent metabolic syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Age at transplant (years)**</td>
<td>1.079</td>
<td>1.006-1.158</td>
</tr>
<tr>
<td>BMI &gt;85th percentile at transplant</td>
<td>9.368</td>
<td>4.345-20.200</td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>2.206</td>
<td>1.096-4.439</td>
</tr>
</tbody>
</table>

*Model included age, gender, race, etiology of renal disease, type of immunosuppression regimen (steroid-sparing versus steroid based), BMI group, and graft function. **OR per year of increased age.
Figure 1: Selection of study patients. *Includes 2 patients with liver/kidney transplants, 2 deaths, and 5 patients who were excluded due to enrollment in experimental immunosuppressive trial.
Figure 2: Frequency of individual criteria for metabolic syndrome among all patients, pre-transplant versus post-transplant. * P <0.001 compared to pre-transplant prevalence.
Figure 3: A) Frequency of individual criteria for metabolic syndrome among lean patients (BMI<25kg/m² and BMI <85th percentile at both time points), at time of transplant versus 1-year post transplant. B) Frequency of individual criteria for metabolic syndrome among non-lean patients (BMI>25kg/m² or BMI >85th percentile one year post-transplant). * p <0.01 compared to pre-transplant prevalence.
Figure 4: Distribution of LVMI (gm/m\(^{2.7}\)) by metabolic syndrome status
Figure 5: Distribution of LV geometry by metabolic syndrome status. *p<0.05 compared to frequency of eccentric LVH in patients without metabolic syndrome.