Race and Electronically Measured Adherence to Immunosuppressive Medications after Deceased Donor Renal Transplantation

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Nonadherence to immunosuppressive medications may partly explain the worse allograft outcomes among black recipients of renal transplants. In a prospective cohort study of recipients of deceased donor renal transplants, microelectronic cap monitors were placed on bottles of one immunosuppressive medication to (*1*) measure average daily percentage adherence during the first posttransplantation year and (2) determine the factors associated with adherence. A total of 278 transplant recipients who provided sufficient microelectronic adherence data were grouped into four categories of average daily percentage adherence: 95 to 100% adherence (41.0% of patients), 80 to 95% adherence (32.4%), 50 to 80% adherence (12.9%), and 0 to 50% adherence (13.7%). In the unadjusted ordinal logistic regression model, black race was associated with decreased adherence (odds ratio [OR], 0.43; 95% confidence interval [CI], 0.26 to 0.72; $P = 0.001$). Cause of renal disease, Powerful Others health locus of control, transplant center, and dosing frequency were also associated with adherence. After adjustment for transplant center and dosing frequency, the association between black race and decreased adherence was substantially attenuated (OR, 0.65; 95% CI, 0.38 to 1.14, $P = 0.13$). Transplant center ($P = 0.003$) and increased dosing frequency (OR, 0.43; 95% CI, 0.22 to 0.86, for three or four times per day dosing; OR, 2.35; 95% CI, 1.01 to 5.45, for daily dosing; *versus* two times per day dosing; $P = 0.003$) remained independently associated with adherence. Other baseline demographic, socioeconomic, medical, surgical, and psychosocial characteristics were not associated with adherence. The transplant center and dosing frequencies of immunosuppressive medications are associated with adherence and explain a substantial proportion of the race–adherence relationship.

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Recipients of renal transplants risk premature allograft failure if they do not adhere to prescribed immunosuppressive medication regimens. Unfortunately, up to 50% of renal transplant recipients are nonadherent (1–4), a spectrum of behaviors that range from missing occasional doses to consistently missing all medication doses. Decreased adherence to immunosuppressive medications is associated with acute rejection (5,6) and seven-fold higher odds of allograft failure (1). Decreased adherence commonly causes late allograft loss (7) and precedes more than one third of allograft failures (1).

Rates of acute rejection and allograft failure are higher among blacks than nonblacks (8–15). Nonadherence may contribute to this racial disparity, given that several studies report decreased adherence among black transplant recipients (2,7,16–18). Low socioeconomic status, however, is also associated with decreased adherence and may partly explain the apparently decreased adherence among black transplant recipients (16,17). Largely unexplored factors surrounding the delivery and provision of health care may also help to explain decreased adherence among blacks.

Microelectronic event monitoring is considered the most valid, reliable, and sensitive method available for measuring adherence (19–23). In microelectronic monitoring, microprocessors embedded in medicine bottle caps record the time and duration of each cap opening. Each opening is assumed to correspond to ingestion of the medication. Unlike other methods of determining adherence, microelectronic monitoring permits counting of missed doses, calculation of the time between doses, and assessment of patterns of poor adherence (19).

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In this prospective cohort study of recipients of deceased donor renal transplants, we used microelectronic monitoring to (*1*) measure adherence to immunosuppressive medications and (*2*) determine the factors associated with adherence. We sought to confirm the previously reported relationship between race and adherence (2,7,16–18) and determine the factors that may explain this relationship.

Materials and Methods

Study Design and Procedures

Between April 1998 and November 2001, we enrolled recipients of deceased donor renal transplants into a prospective cohort study. Patients were recruited at the time of transplantation from eight centers served by the Gift of Life Donor Program in eastern Pennsylvania: Albert Einstein Medical Center, Hahnemann University Hospital, the Hospital of the University of Pennsylvania, and Thomas Jefferson University Hospital (Philadelphia, PA); Geisinger Medical Center (Danville, PA); Hershey Medical Center (Hershey, PA); Lehigh Valley Hospital Center (Allentown, PA); and Lankenau Hospital (Wynnewood, PA). At these centers, patients who were ≥18 yr of age and had received a deceased donor renal transplant were eligible for this study. The study protocol was approved by the human subjects Institutional Review Board at each participating transplant center. Informed consent was obtained from each study participant.

During the initial transplant hospitalization, study participants were interviewed regarding their demographic, socioeconomic, and medical characteristics. Race was determined by self-report. After discharge, participants underwent initial telephone interviews. At 6-mo intervals, study personnel examined participants' inpatient and outpatient medical records and conducted follow-up telephone interviews.

All medical management, including changes to immunosuppressive regimens, was left to the discretion of patients' medical providers. Study data, including measures of medication adherence, were not shared with study participants or their medical providers.

Baseline Psychosocial Information

During the initial posttransplantation telephone interview, patients were administered the Transplant Stress Questionnaire (24), Social Support Appraisal Scale (25), Center for Epidemiologic Studies–Depression Scale (26), Multidimensional Health Locus of Control Scale-Form B (MHLC-B) (27), and Medical Outcomes Study 12-Item Short-Form Health Survey (28,29) to provide baseline measurements of psychosocial factors possibly associated with subsequent medication adherence (Table 1). Patients were also asked whether they were experiencing any side effects from their medications.

Measurement of Adherence Using Microelectronic Event Monitoring

We measured adherence using the electronic Drug Exposure Monitor (eDEM) cap (AARDEX, Ltd., Zug, Switzerland), an electronic cap monitor that records the date and time of each opening and closing of the medication bottle. In each patient, one immunosuppressive medication was monitored at any given time, chosen from the following: mycophenolate mofetil (MMF), tacrolimus, prednisone, azathioprine, and sirolimus.

The eDEM caps were mailed to patients shortly after the initial transplant hospitalization. Patients were asked to return the caps to the study coordinating center every 6 mo. Adherence data were down-

Table 1. Psychosocial instruments administered to study participants during baseline telephone interview

Instrument	Measured Domains	No. of Items	Item Scaling and Scoring	Instrument Scoring
Transplant Stress Questionnaire (TSQ)	Perceived stressfulness of transplant-related issues	12[a]	Ordinal, five-point scales; higher scores signify increased stress	Total score
Social Support Appraisal (SS-A) Scale	Patients' perceptions that their social needs are being met	23	Ordinal, four-point scales; higher scores signify greater perceived social support	Total score, Family subscore (eight items), Friends subscore (seven items)
Center for Epidemiologic Studies—Depression (CES-D) Scale	Depressive symptoms within past week, focusing on affective mood	20	Ordinal, four-point scales (0 to 3); higher scores signify more depressive symptoms	Total score (≥16 signifies depression)
Multidimensional Health Locus of Control (MHLC) Scale-Form B	Patients' beliefs regarding who or what controls and influences their health	18	Ordinal, six-point scales (1 to 6); Higher scores signify that patients believe that health and illness depend upon that locus	Internal subscore (six items), Powerful Others subscore (six items), Chance subscore (six items)
Medical Outcomes Study 12-item Short-Form Health Survey (SF-12)	Health status	12	Ordinal; higher scores signify better health	Physical Component Summary, Mental Component Summary

[a]Original TSQ had 17 items.

loaded from the caps, which then were returned to the patients. When a patient's medical providers discontinued the monitored medication, the patient was instructed to use the microelectronic cap on another immunosuppressive medication from the list above.

Definition and Calculation of Adherence

For each patient, we calculated adherence starting from the second day of microelectronic cap use or the day after the initial telephone interview, whichever occurred later. Patients with fewer than 14 d of usable microelectronic data (*e.g.*, from nonuse of the caps) were excluded from the analysis. For all others, adherence was measured continuously until 12 mo posttransplantation, patient death, or patient withdrawal from the study, whichever occurred first. We excluded study days from adherence calculations when (*1*) the eDEM cap malfunctioned, (*2*) the cap memory was saturated, (*3*) the cap was returned to the study center for data downloading, (*4*) the patient was hospitalized (determined from medical records and patient interviews), or (*5*) the patient seemed to use a partitioned pillbox rather than the electronically monitored bottle. We abandoned initial plans to use semiannual telephone interview data to identify pillbox use, because patients were unable to recall changes in pillbox use over the previous interval, electronic data often showed frequent cap openings during days of reported pillbox use, and patients not reporting pillbox use sometimes displayed data patterns consistent with pillbox use. Instead, we created a data-based definition of pillbox use from two algorithms that we formulated before performing the adherence analyses. First, we divided each patient's study period into nonoverlapping 7-d intervals. When there were fewer than two total cap openings during any two consecutive 7-d intervals, we excluded that 14-d period from adherence calculations, as a result of presumed pillbox use. Second, we divided the study period into rolling, overlapping 7-d intervals. When there were 5 consecutive days without cap use during any rolling 7-d period, we excluded that 7-d period from adherence calculations, as a result of presumed pillbox use.

For each day included in adherence analysis, we calculated the percentage of prescribed doses taken by a patient. On the basis of this daily percentage adherence from each of the patient's eligible study days, we calculated the average (mean) daily percentage adherence. We used average daily percentage adherence as our primary measure of adherence.

Statistical Analyses

Initial analyses were descriptive. Continuous variables were expressed as means ± SD or as medians with 25 to 75% ranges; their values across groups were compared using unpaired *t* test or Wilcoxon rank-sum tests, as appropriate. Categorical variables were expressed as proportions; their comparisons used χ^2 tests.

We grouped study participants into four ordinal categories of average daily percentage adherence, each of roughly equal size: 0 to 50%, >50 to 80%, >80 to 95%, and >95 to 100%. We also treated adherence as a binary outcome, using cutpoints of average daily percentage adherence of 50, 80, or 95%.

To determine the factors that were associated with adherence, we fit a multivariable ordinal logistic regression model using the proportional odds model (30,31). First, we performed unadjusted analyses to examine the association of adherence with demographic, socioeconomic, medical, surgical, and psychosocial characteristics. Factors for which the unadjusted odds ratios (OR) had an associated $P < 0.20$ were eligible for inclusion in the multivariable model. Second, we manually fitted a parsimonious multivariable model, using a backward, stepwise strategy, with $P < 0.10$ as the inclusion criteria. We confirmed the proportional odds assumption using multiplicative interaction terms (to test whether the OR for one factor were consistent across levels of the other factors) and binary logistic regression models (to ensure the similarity of the OR from the binary and ordinal logistic regression models).

Analyses were performed using SAS statistical software, version 8.1 (SAS Institute, Cary, NC). All *P* values were two-sided, with $P < 0.05$ considered statistically significant.

Results

Patient Sample

Of the 829 recipients of deceased donor renal transplants enrolled in the cohort study, 278 (33.5%) were included in the adherence analysis. The 551 excluded patients were deemed ineligible for the analysis for various reasons (Figure 1) and differed from the 278 included patients (Table 2). Black race, maintenance dialysis before transplantation, and delayed allograft function were more common among the included patients. Renal disease cause, education level, and initial choice of calcineurin inhibitor differed between included and excluded patients.

Baseline Characteristics

The baseline demographic, medical, and surgical characteristics of the 278 study patients differed according to race (Table 2). Among blacks (as compared with nonblacks), dosing frequency of the initially monitored immunosuppressive was more likely to be three or four times per day, although this difference was not statistically significant by traditional criteria.

Results from the initial, posttransplantation telephone interview are shown in Table 3. Transplant-related stress, as measured by the abbreviated Transplant Stress Questionnaire, was

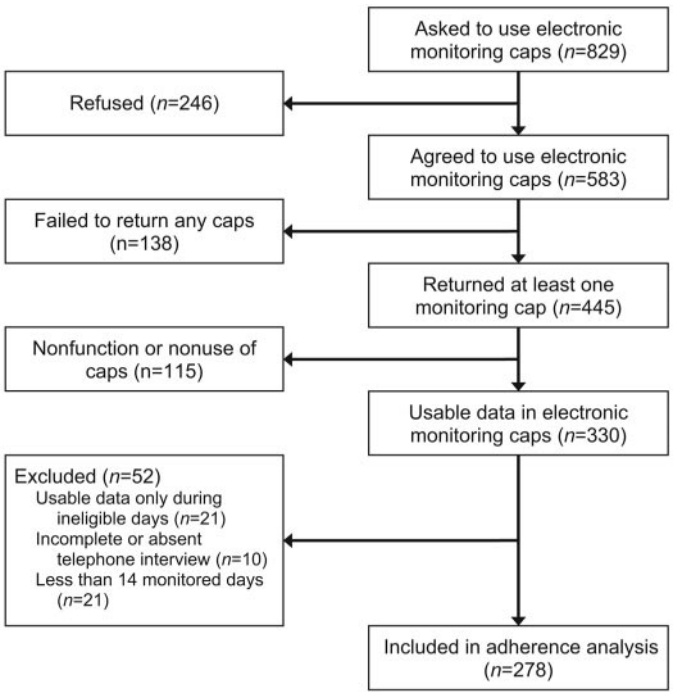

Figure 1. Enrollment and flow of participants through the study.

Table 2. Baseline demographic, medical, and surgical characteristics at the time of transplantation[a]

	Eligible Patients		*P* Value[b]	Eligible Patients Included in Analysis		*P* Value[c]
	Excluded from Analysis	Included in Analysis		Blacks	Nonblacks	
No. of patients	551	278	—	68	210	—
Median age (yr [25—75%])	49 (39 to 59)	48 (39 to 57)	0.25	48 (40 to 57)	47 (38 to 57)	0.83
Black race (%)	34.7	24.5	0.003	—	—	—
Male (%)	59.7	61.2	0.69	67.7	59.1	0.21
Highest education level (%)			0.009			0.85
through high school	58.4	47.8		50.0	47.1	
any college	35.2	44.2		41.2	45.2	
any post-college education	6.5	7.9		8.8	7.6	
Marital status (%)			0.55			0.39
married or cohabiting	56.3	59.4		55.9	60.5	
widowed or divorced	18.8	15.8		13.2	16.7	
single	25.0	24.8		30.9	22.9	
Employed full time or part time (%)	29.7	28.4	0.70	26.5	29.1	0.68
Annual income (%)			0.29			0.15
<$20,000	44.3	40.4		50.8	37.1	
$20,000 to <$40,000	25.1	25.9		19.7	27.8	
≥$40,000	30.6	33.7		29.5	35.1	
Cause of renal disease (%)			0.008			0.002
diabetes	32.7	30.9		30.9	31.0	
hypertension	21.8	15.5		29.4	11.0	
glomerulonephritis	18.0	28.4		26.5	29.1	
cystic kidney disease	9.1	8.3		2.9	10.0	
other or unknown	18.5	16.9		10.3	19.1	
History of diabetes (%)	40.2	35.6	0.20	33.8	36.2	0.72
On maintenance dialysis (%)	93.3	87.4	0.006	98.5	83.8	0.002
if yes, then median years on dialysis (25—75%)	3.0 (1.6 to 4.8)	2.6 (1.4 to 4.3)	0.12	3.5 (2.5 to 4.7)	2.4 (1.2 to 4.1)	0.001
Number of HLA mismatches (%)			0.25			<0.001
0	9.6	8.4		4.8	9.6	
1 to 2	13.9	19.1		2.4	24.3	
3 to 4	46.9	49.4		54.8	47.8	
5 to 6	29.7	23.0		38.1	18.4	
Median length of initial transplant hospital stay (d [25—75%])	6 (5 to 9)	7 (5 to 10)	0.94	7 (5 to 11)	6 (5 to 10)	0.13
Occurrence of delayed allograft function (%)	43.7	31.7	0.001	50.0	25.7	<0.001
In-hospital rejection (%)	5.6	6.8	0.48	5.9	7.1	0.72
Previous renal transplant (%)	14.3	17.3	0.26	14.9	18.1	0.55
Initial calcineurin inhibitor (%)			0.001			0.46
cyclosporine	56.4	46.8		44.1	47.6	
tacrolimus	39.4	51.8		52.9	51.4	
none	4.2	1.4		2.9	1.0	
Immunosuppressive medication initially monitored (%)			—			0.79
MMF	—	82.7	—	86.8	81.4	
tacrolimus	—	7.9	—	5.9	8.6	
prednisone	—	8.3	—	7.4	8.6	
azathioprine	—	0.7	—	0.0	1.0	
sirolimus	—	0.4	—	0.0	0.5	
Original dosing frequency of initially monitored immunosuppressive medication (%)[d]			—			0.08
one time per day	—	10.1	—	7.4	11.0	
two times per day	—	70.5	—	66.2	71.9	
three or four times per day	—	19.4	—	26.5	17.1	
Initial dose of MMF, when MMF was monitored drug (%)						0.02
≤1000 mg/d	—	28.4	—	15.5	32.8	
>1000 to 1500 mg/d	—	6.6	—	8.6	5.9	
>1500 mg/d	—	65.1	—	75.9	61.4	

[a]MMF, mycophenolate mofetil.
[b]Comparing patients who were included in the adherence analysis *versus* patients who were excluded from the adherence analysis.
[c]Comparing black patients who were included in the adherence analysis *versus* nonblack patients who were included in adherence analysis.
[d]Refers to the dosing frequency for the first day included in the adherence analysis.

significantly higher in nonblacks than in blacks. Other psychosocial characteristics were similar between blacks and nonblacks.

Adherence

During their first posttransplantation year, the 278 study participants provided a median of 204 d (interquartile range, 114 to 291 d) of usable electronic adherence data. Table 4 shows patients' average daily percentage adherences. The median average daily percentage adherence was 92.6% (interquartile range, 77.0 to 97.7%). During follow-up, the monitored medication changed in 15 (5.4%) patients (six black, nine nonblack).

Ordinal Logistic Regression

Unadjusted Analysis

In the unadjusted, ordinal logistic regression model (Table 5), black race was associated with decreased adherence (OR, 0.43; 95% confidence interval [CI], 0.26 to 0.72; $P = 0.001$). Transplant center was associated with adherence ($P < 0.0001$). Renal disease cause, original dosing frequency of the initially monitored medication, and the Powerful Others subscore of the MHLC-B questionnaire were also associated with adherence ($P < 0.20$). Higher subscores on the Powerful Others domain of the MHLC-B reflect an increased belief that one's health is controlled by other people, particularly health care providers. No other baseline demographic, socioeconomic, medical, surgical, or psychosocial characteristics were associated with adherence.

Adjusted Model

In the adjusted, multivariable ordinal logistic regression model (Table 6), only transplant center and original dosage frequency of the initially monitored medication were independently associated with adherence. Neither renal disease cause nor the Powerful Others subscore was statistically significant in the adjusted model. Adjustment for transplant center and initial dosage frequency attenuated the race–adherence association so that black race was no longer associated with a statistically significant decrease in adherence (OR, 0.65; 95% CI, 0.38 to 1.14; $P = 0.13$). Multiplicative interaction terms for the relationships between race and dose frequency ($P = 0.12$) and race and transplant center ($P = 0.35$) were NS.

To determine whether our findings were an artifact of the algorithms that excluded days of presumed pillbox use, we applied neither algorithm, only the first algorithm, and then only the second algorithm to the original adherence data and repeated the unadjusted and adjusted analyses. The final multivariable model remained unchanged regardless of which pillbox algorithm (if any) was applied.

Discussion

In this prospective, multicenter cohort study, more than one quarter of recipients of deceased donor renal transplants were <80% adherent to immunosuppressive medications. Black race was strongly associated with lower levels of adherence (unadjusted OR, 0.43; $P = 0.001$). In the multivariable analysis, however, only transplant center and dosing frequency were independently associated with adherence, and adjustment for transplant center and dosing frequency substantially attenuated the race–adherence relationship. This attenuation suggests that center-related characteristics and prescription of immunosuppressive regimens with higher dosing frequencies explain much of the decreased adherence among blacks.

In this study, more frequent dosing schedules were associated with decreased adherence and partly explained the lower adherence observed among blacks. Increased dosing frequency

Table 3. Baseline psychosocial characteristics, at the time of initial telephone interview

	All Included Patients ($n = 278$)	Blacks ($n = 68$)	Nonblacks ($n = 210$)	P Value[a]
Abbreviated TSQ (median [25–75%])	22 (17 to 28)	19 (15 to 26)	23 (18 to 29)	0.007
SS-A (median [25–75%])				
Total	78 (71 to 85)	78 (69 to 84)	79 (72 to 86)	0.47
Family	29 (26 to 31)	28 (25 to 31)	29 (26 to 31)	0.68
Friends	23 (21 to 27)	23 (21 to 26)	23 (21 to 27)	0.29
CES-D				
Depressed (%)	17.5	13.4	18.8	0.32
MHLC-B (median [25–75%])				
Internal	26 (24 to 29)	27 (24 to 30)	26 (24 to 29)	0.77
Powerful Others	26 (22 to 29)	26 (21 to 30)	26 (23 to 29)	0.54
Chance	18 (15 to 22)	18 (14 to 22)	18 (15 to 22)	0.54
SF-12 (median [25–75%])				
physical component	36.4 (31.0 to 43.7)	38.0 (30.5 to 45.4)	35.9 (31.3 to 42.6)	0.40
mental component	57.4 (50.3 to 61.2)	57.6 (50.8 to 61.1)	57.4 (50.3 to 61.2)	0.57
Experiencing side effects from medications (%)	58.4	56.3	59.0	0.69

[a]Comparing black patients who were included in adherence analyses versus nonblack patients who were included in adherence analyses.

Table 4. Average daily percentage adherence

Average Daily Percentage Adherence	All Patients (n = 278)	Blacks[a] (n = 68)	Nonblacks[a] (n = 210)
>95 to 100%	114 (41.0%)	16 (23.5%)	98 (46.7%)
>80 to 95%	90 (32.4%)	27 (39.7%)	63 (30.0%)
>50 to 80%	36 (12.9%)	11 (16.2%)	25 (11.9%)
0 to 50%	38 (13.7%)	14 (20.6%)	24 (11.4%)

[a] $P = 0.002$ for difference between blacks and nonblacks.

has been associated with decreased adherence to most types of medications (32), including antiepileptic (33), antihypertensive (34), HIV antiretroviral (35), and antipsychotic (36) drugs. Studies of adherence after renal transplantation, however, have not examined the impact of dosing frequency, with the exception of one preliminary study of 25 renal transplant recipients (23). In patients of all races, prescription of immunosuppressive medications as once- or twice-daily drugs, when feasible, may increase adherence. For example, dosing of MMF twice daily, instead of three times per day, may lead to increased adherence. Furthermore, a recent study reported that once-daily dosing of tacrolimus may provide safe and equivalent drug exposure to traditional twice-daily dosing, potentially increasing patient adherence (37). Admittedly, gastrointestinal side effects may preclude twice-daily dosing of MMF, and pharmacogenetic differences may preclude once-daily dosing of tacrolimus among blacks. Nevertheless, reductions in dosing frequency may help patients to adhere to prescribed medication regimens.

Our results also suggest that center-related characteristics strongly influence patient adherence. To our knowledge, previous studies have not documented between-center differences in medication adherence. Although possible, it is unlikely that patients at some transplant centers were intrinsically less adherent than patients at other centers, especially after adjusting for the demographic, socioeconomic, psychosocial, and other variables collected by our study. The more likely explanation is that "transplant center" serves as a proxy for characteristics associated with each center's transplant program, such as staffing levels, the "cultural competency" of transplant care providers, patient satisfaction with the patient–provider relationship, the frequency and quality of patient contact with providers, racial concordance between patients and providers, and the effectiveness of patient education provided by the center, among others. Future studies that focus explicitly on between-center differences in patient adherence will be able to examine these characteristics more specifically.

Psychosocial and socioeconomic characteristics were not independently associated with adherence. Furthermore, these characteristics did not explain the association between black race and decreased adherence. Previous studies have linked posttransplantation adherence with stress (4), social support (2), depression (2), health locus of control (2,4,38), health status (38), and annual income (16,17). We carefully measured each of these characteristics and other factors, such as self-perceived health status, and none was associated with adherence in the adjusted model. Racial differences in adherence could not be attributed to differences in psychosocial or socioeconomic factors.

Our study has several strengths. First, we measured adherence prospectively using microelectronic monitors rather than traditional and limited methods, such as drug levels (2), patient self-reports (4,5,38,39), pill counts (40), prescription refill records (3,41), clinic attendance, or combinations of these measures (2,7,16,18). Microelectronic monitors provide higher quality adherence data than these traditional methods (19–22). Second, we enrolled patients from eight different transplant centers, using broad initial inclusion criteria. Most studies to date of posttransplantation adherence have reported data from a single center (2–7,21,38), potentially limiting generalizability and the ability to examine between-center differences in adherence. Third, we enrolled a racially diverse study population, nearly one quarter black, which probably resembles the population followed at many US transplant centers. Fourth, we monitored commonly prescribed immunosuppressive medications, such as MMF and tacrolimus. Other studies have electronically monitored azathioprine (6,23,42,43), which is less commonly prescribed today. Fifth, we used algorithms to determine days of pillbox use and exclude them from the analysis. Previous studies that used microelectronic monitors did not specify how they dealt with possible measurement error stemming from pillbox use. Sixth, we prospectively collected detailed information on demographic, socioeconomic, psychosocial, medical, and surgical variables using, when available, previously validated instruments. We used univariable and multivariable analysis to examine whether these variables were associated with adherence and whether these variables explained the decreased adherence among blacks. Finally, we considered adherence as an ordinal, four-level variable. Most studies have considered medication adherence and "nonadherence" as binary variables (2,3,5,16,17,44), oversimplifications that may also lead to loss of power and precision.

Our study has several limitations. Because our primary study aim was to explore the relationship between race and drug adherence (not possible with an experimental study design), we performed a prospective, observational cohort study. Although we collected extensive data on factors that are potentially associated with adherence, we cannot exclude the possibility that unmeasured or incompletely measured factors may be associated with adherence. In addition, these unmeasured or incom-

Table 5. Unadjusted ordinal logistic regression for associations with adherence[a]

Variable	OR (95% CI)	*P* Value
Age (yr [*versus* <40])		0.50
40 to <50	0.85 (0.47 to 1.51)	
50 to <60	1.34 (0.73 to 2.47)	
≥60	0.96 (0.51 to 1.83)	
Black race (*versus* nonblack)	0.43 (0.26 to 0.72)	0.001
Female (*versus* male)	0.82 (0.52 to 1.27)	0.36
Education (*versus* through high school)		0.68
any college	0.82 (0.52 to 1.28)	
any post-college education	0.93 (0.41 to 2.13)	
Marital status (*versus* married or cohabitating)		0.98
widowed or divorced	0.98 (0.53 to 1.81)	
single	0.94 (0.56 to 1.58)	
Annual income (*versus* <$20,000)		0.42
$20,000 to <$40,000	1.47 (0.83 to 2.60)	
≥$40,000	1.16 (0.69 to 1.96)	
Not employed (*versus* employed)	1.08 (0.67 to 1.74)	0.75
Cause of renal disease (*versus* diabetes)		0.06
hypertension	0.44 (0.23 to 0.86)	
glomerulonephritis	0.84 (0.48 to 1.47)	
cystic	1.59 (0.66 to 3.84)	
other or unknown	0.98 (0.51 to 1.89)	
Diabetes (*versus* no diabetes)	1.25 (0.79 to 1.96)	0.34
Maintenance dialysis before transplant (*versus* no dialysis)	0.99 (0.52 to 1.89)	0.97
No. of HLA mismatches (*versus* 0)		0.70
1 to 2	1.32 (0.42 to 4.08)	
3 to 4	0.85 (0.31 to 2.32)	
5 to 6	1.02 (0.34 to 3.04)	
Length of initial transplant hospital stay (per 1 day)	1.01 (0.96 to 1.07)	0.69
Delayed allograft function	0.80 (0.51 to 1.27)	0.35
In-hospital rejection	1.07 (0.45 to 2.51)	0.88
Previous renal transplant (*versus* no previous transplant)	1.38 (0.77 to 2.47)	0.27
Initial calcineurin inhibitor (*versus* cyclosporine)		0.98
tacrolimus	0.98 (0.63 to 1.51)	
none	1.17 (0.19 to 7.39)	
Dosage frequency of initially monitored immunosuppressive medication (*versus* two times per day)		<0.0001
one time per day	1.66 (0.77 to 3.58)	
three or four times per day	0.29 (0.17 to 0.51)	
Transplant Stress Questionnaire (per 1 point)	1.00 (0.97 to 1.03)	0.94
Social Support Appraisals		
Total score (per 1 point)	1.01 (0.98 to 1.03)	0.65
Family subscore (per 1 point)	1.04 (0.98 to 1.10)	0.25
Friends subscore (per 1 point)	1.00 (0.93 to 1.07)	0.94
CES-D		
Depressed (*versus* not depressed)	0.91 (0.51 to 1.60)	0.73
Health Locus of Control		
Internal (per 1 point)	1.01 (0.96 to 1.07)	0.74
Chance (per 1 point)	0.99 (0.95 to 1.04)	0.72
Powerful Others (per 1 point)	1.05 (1.00 to 1.11)	0.05
SF-12		
physical subscore (per 1 point)	1.01 (0.98 to 1.03)	0.53
mental subscore (per 1 point)	1.00 (0.98 to 1.03)	0.92
Side effects from medications (*versus* no side effects)	0.76 (0.49 to 1.19)	0.23
Transplant center	—	<0.0001

[a]OR, odds ratio; CI, confidence interval.

Table 6. Multivariable ordinal logistic regression for factors associated with adherence

	Unadjusted		Adjusted for Transplant Center Alone[a]		Adjusted for Transplant Center and Dosing Frequency[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Black race (*versus* nonblack race)	0.43 (0.26 to 0.72)	0.001	0.59 (0.34 to 1.02)	0.057	0.65 (0.38 to 1.14)	0.13
Transplant center[a]	—	—	—	<0.0001	—	0.003
Dosing frequency (*versus* two times per day)						0.003
one time per day	—	—	—	—	2.35 (1.01 to 5.45)	
three or four times per day	—	—	—	—	0.43 (0.22 to 0.86)	

[a]OR for individual transplant centers are not presented to preserve the anonymity of the participating transplant centers.

pletely measured factors may help to explain the race–adherence relationship.

Selection bias might have occurred in two ways. First, participants in research studies are typically more adherent to therapy than the general population (45). This bias would have led to overestimation of adherence, but we documented substantial nonadherence among our patients. Selection bias does not explain why >25% of the patients had average daily percentage adherences of 80% or lower, a level associated with increased rates of acute rejection (6). Second, selection bias could have been introduced if poorly adherent blacks were differentially more likely to participate in our study than poorly adherent nonblacks, *versus* a similar comparison among more adherent transplant recipients. Such differential study enrollment is unlikely. Poorly adherent blacks were probably less likely to participate, given low rates of participation in clinical research by blacks (46,47).

Like other methods for assessing adherence, microelectronic monitoring is susceptible to measurement error. Microelectronic monitoring assumes that each cap opening corresponds to ingestion of the prescribed medication dose and that the absence of a cap opening corresponds to a missed dose, but these assumptions may not always hold true. If patients periodically remove medications from their bottles for later ingestion ("pill-pocketing") or use partitioned pillboxes, then microelectronic monitoring may underestimate adherence (48). We minimized underestimation by using algorithms to exclude days of presumed pillbox use. These algorithms may have actually caused a countervailing overestimation of adherence by misclassifying some electronically silent days of nonadherence as days of presumed pillbox use. We cannot exclude the possibility that "pill-pocketing" and other unorthodox medication ingestion behaviors contributed to the decrease in electronically measured adherence to medications that were dosed more than once per day.

This study has other limitations. First, we did not corroborate the microelectronic data with other adherence measures, such as drug levels, pill counts, or prescription refill rates. Second, we did not examine the clinical impact of decreases in electronically measured adherence. Previous studies, however, have already associated decreased adherence with subsequent allograft failure, using both microelectronic (6) and traditional (1,5,40) measures of adherence. Finally, our findings may have limited generalizability. We studied recipients of deceased donor renal transplants during their first year posttransplantation, so our results do not necessarily apply to recipients several years posttransplantation or to recipients of living donor transplants. In addition, study participants were not a random subset of the initial target population. Nevertheless, study results are often generalizable even if the study population is not perfectly representative of the target population (49). Our large, diverse, and multicenter cohort represents well the national renal transplant population. Furthermore, any limits on generalizability would neither introduce bias nor compromise our study's internal validity.

In conclusion, many renal transplant recipients are poorly adherent. The transplant center and dosing frequency are independently associated with adherence and largely explain the lower levels of adherence observed among black recipients. The contribution of higher dosing frequencies to decreased adherence, although previously recognized outside of transplantation, has not been well described in transplantation until now. The association of the transplant center with adherence is novel, and additional studies are needed to elucidate the center-related characteristics that influence adherence, with particular emphasis on those characteristics that are modifiable. Other studies are needed to confirm the association between dosing frequency and adherence to transplant medications, assess the clinical impact of lower levels of electronically measured adherence, and test interventions to improve adherence.

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