

Determinants of Insulin Resistance in Renal Transplant Recipients

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Background. Insulin resistance is considered to play an important role in the development of cardiovascular disease, which limits long-term renal transplant survival. Renal transplant recipients are more insulin-resistant compared with healthy controls. It is not known to date which factors relate to this excess insulin resistance. Therefore, we investigated which factors are related to insulin resistance long-term after renal transplantation.

Methods. All renal transplant recipients at our outpatient clinic with a functioning graft for more than one year were invited to participate. We excluded diabetic recipients. Recipient, donor, and transplant characteristics were collected as putative determinants. We used fasting insulin, homeostasis model assessment index, and McAuley's index as valid estimates of insulin resistance. Linear regression models were created to investigate independent determinants of all indexes.

Results. A total of 483 recipients (57% male, 50±12 years) were analyzed at a median (interquartile range) time of 6.0 (2.6–11.6) years posttransplant. The most consistent determinants across all three indices were body mass index ($P<0.001$), waist-to-hip ratio ($P<0.001$), and prednisolone dose ($P<0.05$). Independent associations were present for total cholesterol ($P<0.001$), high-density lipoprotein cholesterol ($P<0.001$), creatinine clearance ($P<0.05$), recipient age ($P<0.001$), and gender ($P\leq 0.002$). No independent associations were present for transplant-related factors such as acute rejection treatment or cytomegalovirus seropositivity.

Conclusions. Our results indicate that obesity, distribution of obesity, and prednisolone treatment are the predominant determinants of insulin resistance long term after transplantation. Insulin resistance after renal transplantation could be managed favorably by weight and prednisolone dose reduction, which may reduce cardiovascular disease.

Keywords: Renal transplantation, Insulin resistance, Cardiovascular risk factor, Obesity.

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Cardiovascular disease after renal transplantation limits long-term patient survival (1). Both incidence and prevalence of cardiovascular disease are estimated to be five times higher than in the general population (2, 3). Insulin resistance is considered to play an important role in the development of cardiovascular disease (4).

Obesity has been identified as an important determinant of insulin resistance in renal transplant recipients shortly after transplantation (5). However, renal transplant recipients are still more insulin-resistant than healthy con-

trols when matched for body mass index (BMI) and age (6). This suggests that additional transplant-specific determinants contribute to insulin resistance in renal transplant recipients. These include poor physical activity, chronic use of immunosuppressive drugs such as corticosteroids and calcineurin inhibitors, and persistent low-grade inflammatory activity of viral infections, in particular cytomegalovirus (CMV) (5, 7, 8).

A recent study indicated that corticosteroid dose as well as active CMV infections are associated with insulin resistance immediately after transplantation (5). However, it is unknown to which extent both traditional, nontransplant-related factors (such as obesity) and transplant-related factors contribute to insulin resistance long-term after transplantation. Therefore, we investigated the determinants of insulin resistance in renal transplant recipients using validated insulin resistance indexes (5, 9, 10).

PATIENTS AND METHODS

Research Design and Subjects

To investigate determinants of insulin resistance, we invited all adult renal transplant recipients from our outpa-

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TABLE 1. Recipient- and transplant-related characteristics

No.	483
Recipient demographics	
Age, y	50±12
Male gender, n (%)	275 (57)
History of cardiovascular disease	
Myocardial infarction, n (%)	37 (8)
Transient ischemic attack or cerebrovascular accident, n (%)	21 (4)
Body composition	
Body mass index, kg/m ²	25.6±4.1
Waist circumference, cm	95.6±13.1
Waist-to-hip ratio	0.97±0.10
Posttransplant weight gain, kg	2.2±6.3
Physical exercise	
Metabolic equivalents per week	7204 (1620–17,402)
Blood pressure and medication	
Systolic blood pressure, mm Hg	151±22
Diastolic blood pressure, mm Hg	90±10
Angiotensin-converting enzyme inhibitor, n (%)	159 (33)
β-blocker, n (%)	299 (62)
Lipids	
Cholesterol, mmol/L	5.6 (5.0–6.2)
H-gH-density lipoprotein cholesterol, mmol/L	1.1 (0.9–1.3)
Nonhigh-density lipoprotein cholesterol, mmol/L	4.5 (3.9–5.2)
Triglycerides, mmol/L	1.9 (1.4–2.5)
Statin, n (%)	229 (47)
Substance use	
Alcohol, n (%)	
None	218 (45)
1–4/mo	72 (15)
>2/wk	193 (40)
Smoking, n (%)	
Current smokers	112 (23)
Nonsmokers	371 (77)
Inflammation	
C-reactive protein, mg/L	1.9 (0.8–4.4)
Insulin resistance indices	
Fasting insulin, μU/mL	10.3 (7.7–14.1)
Homeostasis Model Assessment	2.02 (1.49–2.92)
McAuley's index	6.1±1.2
Glucose, mmol/L	4.5±0.6
Donor demographics	
Age, y	38±16
Male gender, n (%)	260 (54)
Renal allograft function	
Serum creatinine, μmol/L	150±60
Creatinine clearance, mL/min	62±23
Creatinine excretion, mmol/24 h	12.2±3.6
Proteinuria, g/24 h	0.2 (0.0–0.5)

TABLE 1. Continued

Acute rejection treatment	
High-dose corticosteroids, n (%)	150 (31)
Other rejection therapy, n (%)	72 (15)
Cytomegalovirus status	
Cytomegalovirus seropositivity before transplantation	
Recipient, n (%)	223 (46)
Donor, n (%)	255 (53)
Cytomegalovirus infection	
No infection, n (%)	255 (53)
Primary infection, n (%)	95 (20)
Secondary infection, n (%)	113 (27)
Cytomegalovirus status at inclusion	
Seropositive recipients, n (%)	349 (72)
Immunosuppression	
Prednisolone dose, mg/d	10.0 (7.5–10.0)
Cyclosporine, n (%)	304 (63)
Tacrolimus, n (%)	68 (14)
Mycophenolate mofetil, n (%)	207 (43)
Azathioprine, n (%)	159 (33)

tient clinic who survived the first year after transplantation with a functioning allograft, as described in detail elsewhere (11, 12). A total of 606 renal transplant recipients signed written informed consent, from an eligible 847 (72% consent rate). The group that did not sign informed consent was comparable with the group that signed informed consent with respect to age, gender, BMI, serum creatinine, creatinine clearance, and proteinuria. Excluded from analysis were 106 recipients with diabetes mellitus (defined as a fasting plasma glucose ≥ 7.0 or use of antidiabetic medication [13]). Also excluded were an additional 17 recipients who had received a combined transplantation (kidney–pancreas or kidney–liver), leaving 483 nondiabetic renal transplant recipients for analysis. The Institutional Review Board approved the study protocol (METc 2001/039). Funding sources had neither a role in the collection and analysis of data nor in publication of the manuscript.

Renal Transplant Characteristics

Relevant transplant characteristics were taken from the Groningen Renal Transplant Database. This database holds information on all renal transplantations performed at our center since 1968, including primary and secondary infection with CMV. Current medication was taken from the medical record. Standard immunosuppressive treatment was described previously (11, 12)

Putative Determinants of Insulin Resistance

BMI, waist circumference, and blood pressure were measured as described previously (11, 12). Smoking status and alcohol consumption were assessed with a self-report questionnaire (14). Physical activity was assessed during the past six months with the Tecumseh Occupational Activity Questionnaire and Minnesota Leisure Time Physical Activity Questionnaire (15). Physical activity is expressed as meta-

TABLE 2. Univariate analyses of renal recipient-related characteristics with fasting insulin, Homeostasis Model Assessment, and McAuley's index

	Fasting insulin		Homeostasis Model Assessment		McAuley	
	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value
Recipient demographics						
Age, y	-0.10	0.04	-0.09	0.06	0.03	0.58
Gender male, %	-0.03	0.46	0.01	0.97	-0.01	0.75
History of cardiovascular disease						
Myocardial infarction, n (%)	0.01	0.78	0.02	0.74	-0.03	0.54
Transient ischemic attack or cerebrovascular accident, n (%)	0.08	0.07	0.07	0.11	-0.08	0.08
Body composition						
Body mass index, kg/m ²	0.40	<0.001	0.40	<0.001	-0.40*	<0.001*
Waist circumference, cm	0.36	<0.001	0.36	<0.001	-0.42	<0.001
Waist-to-hip ratio	0.29	<0.001	0.31	<0.001	-0.40	<0.001
Posttransplant weight gain, kg	0.20	<0.001	0.20	<0.001	-0.20*	<0.001*
Physical exercise						
Metabolic equivalents per week	-0.06	0.20	-0.05	0.26	0.08	0.11
Blood pressure						
Systolic blood pressure, mm Hg	-0.05	0.29	-0.04	0.35	-0.06	0.19
Diastolic blood pressure, mm Hg	-0.01	0.88	-0.01	0.85	-0.07	0.12
Angiotensin-converting enzyme inhibitor, %	0.15	0.001	0.15	<0.001	-0.15	0.001
β -blocker, %	0.05	0.23	0.08	0.08	-0.13	0.004
Lipids						
Cholesterol, mmol/L	-0.11	0.01	-0.10	0.04	-0.14	0.002
High-density lipoprotein cholesterol, mmol/L	-0.28	<0.001	-0.28	<0.001	0.40	<0.001
Nonhigh-density lipoprotein cholesterol, mmol/L	-0.03	0.59	-0.01	0.86	-0.27	<0.001
Triglycerides, mmol/L	0.21	<0.001	0.24	<0.001	—	—
Statin, %	0.07	0.13	0.07	0.13	-0.19	<0.001
Substance use						
Alcohol, %	0.12	0.007	-0.07	0.16	0.09	0.06
Current smoking, %	-0.05	0.25	-0.02	0.67	-0.01	0.88
Glucose, mmol/L	0.21	<0.001	—	—	-0.23	<0.001
Inflammation						
C-reactive protein, mg/L	0.05	0.27	0.07	0.14	-0.10	0.03
Donor demographics						
Age, y	-0.01	0.87	0.01	0.94	-0.02	0.66
Male sex, %	0.03	0.52	0.03	0.55	-0.02	0.63
Renal allograft function						
Serum creatinine, μ mol/L	-0.02	0.79	0.01	0.88	-0.10	0.03
Creatinine clearance, mL/min	0.10	0.02	0.09	0.05	-0.08	0.10
Creatinine excretion, mmol/24 h	0.11	0.02	0.10	0.02	-0.02	0.61
Proteinuria, g/24 h	0.02	0.69	0.06	0.23	-0.09	0.04
Acute rejection treatment						
High-dose corticosteroids, %	-0.08	0.10	-0.05	0.28	-0.01	0.88
Other rejection therapy, %	0.04	0.38	0.03	0.48	-0.04	0.36
Cytomegalovirus status						
Cytomegalovirus seropositivity before transplantation						
Recipient, %	-0.03	0.47	0.04	0.42	-0.01	0.76
Donor, %	-0.01	0.94	0.01	0.82	-0.04	0.40
Primary or secondary cytomegalovirus infection, %	0.05	0.23	0.05	0.23	-0.07	0.14
Cytomegalovirus seropositive at inclusion, %	-0.05	0.27	-0.05	0.28	-0.05	0.31

TABLE 2. Continued

	Fasting insulin		Homeostasis Model Assessment		McAuley	
	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value
Immunosuppression						
Prednisolone dose, mg/d	0.09	0.06	0.10	0.03	-0.09	0.05
Cyclosporine, %	-0.03	0.50	-0.04	0.40	-0.07	0.13
Trough-level, $\mu\text{g/L}$	0.05	0.37	0.05	0.40	-0.04	0.47
Tacrolimus, %	0.07	0.11	0.08	0.07	0.05	0.24
Trough-level, $\mu\text{g/L}$	-0.11	0.39	-0.07	0.58	0.17	0.17
Mycophenolate mofetil, %	0.01	0.90	0.01	0.87	0.06	0.18
Azathioprine, %	0.04	0.35	0.04	0.37	-0.05	0.32

Betas are reported as standardized betas. Significant effect modification by gender is indicated by an asterisk (*) for body mass index and posttransplant weight gain for McAuley's index.

bolic equivalents per week. One metabolic equivalent is approximately 3.5 mL of oxygen per kilogram body weight per minute, the energy expenditure of the average adult for sitting quietly.

Insulin Resistance Indexes

We used fasting insulin, Homeostasis Model Assessment (HOMA), and McAuley's index as surrogate estimates of insulin resistance (16–18). These indices have recently been validated in our own renal transplant population (10) as well as in a renal transplant population comparable to ours (5, 9). HOMA was calculated as: (glucose [mmol/L] \times insulin [$\mu\text{U/mL}$])/22.5 and McAuley's index was calculated as: $\exp(2.63 - 0.28 \ln[\text{insulin } (\mu\text{U/mL})] - 0.31 \ln[\text{triglycerides (mmol/L)}])$.

Fasting insulin was determined using an AxSym autoanalyzer (Abbott Diagnostics). The intra- and interassay coefficients of variation at 8.7 mU/L are 2.6% and 2.9%, respectively. At 42.2 mU/L, the intra- and interassay coefficients are 4.1% and 2.1%, respectively. The assay shows virtually no crossreactivity with proinsulin (0.016% at 10^6 pg/mL).

Laboratory Measurements

Blood was drawn after an 8- to 12-hour overnight fasting period. Serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL) were assessed as described previously (11). Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol (19). High-sensitivity C-reactive protein was assessed as described previously (12). Renal allograft function was assessed by 24-hour urinary creatinine clearance. Muscle mass was assessed by 24-hour creatinine excretion. Cytomegalovirus immunoglobulin G (IgG) was assessed by routine enzyme-linked immunosorbent assay (20). A detectable CMV IgG titer indicated seropositivity.

Statistical Analysis

Data was analyzed with SPSS version 12.0 (SPSS Inc.). Parametric parameters are given as means \pm standard deviation, whereas nonparametric parameters are given as median (interquartile range). Skewed data were normalized by logarithmic transformation in all analyses. χ^2 and Student *t* test were used to test gender differences among categorical and

continuous variables. A two-sided *P* value less than 0.05 indicated statistical significance. Regression coefficients are given as standardized betas. Tolerance statistics >0.20 for variables in multivariate analyses were considered to indicate that assumptions of colinearity were not violated.

Univariate linear regression analyses were used to explore the impact of each putative determinant on fasting insulin, HOMA, and McAuley's index. We additionally analyzed the determinants of insulin resistance for gender interaction, because such an interaction has been noted previously (21). Finally, we performed multivariate linear regression analyses to investigate which determinants were independently associated with the insulin resistance indices. To this purpose, all putative factors that were univariately associated with any index (at a *P* value <0.1) were included in a backward linear regression model. Also included in multivariate analyses were age and gender of the recipient as well as any significant interaction term with gender. The impact of the determinants was compared by the magnitude of the standardized regression coefficients.

RESULTS

We investigated 483 renal transplant recipients at a median time of 6.0 (2.6–11.6) years posttransplant (57% male, 50 ± 12 years, 85% cadaveric transplants). Table 1 shows the further characteristics of the study population.

Table 2 shows the associations between the study characteristics and the insulin resistance indices. Measures of obesity had the strongest associations with all three indices. Obesity was negatively associated with McAuley's index because it reflects insulin sensitivity and is an inverse measure of insulin resistance. Figures 1A and 1B show that both increasing BMI and increasing waist-to-hip ratio are associated with increasing fasting insulin concentrations. An interaction was present between gender and BMI for McAuley's index showing that the effect of BMI on insulin resistance was stronger in men. The three indices were also univariately associated with HDL cholesterol, total cholesterol, triglycerides, and fasting glucose concentrations. Blood pressure was not associated with insulin resistance in contrast to the use of angiotensin-converting enzyme inhibitors. Use of beta-blockers was only associated with McAuley's index. Inflammation, as reflected by

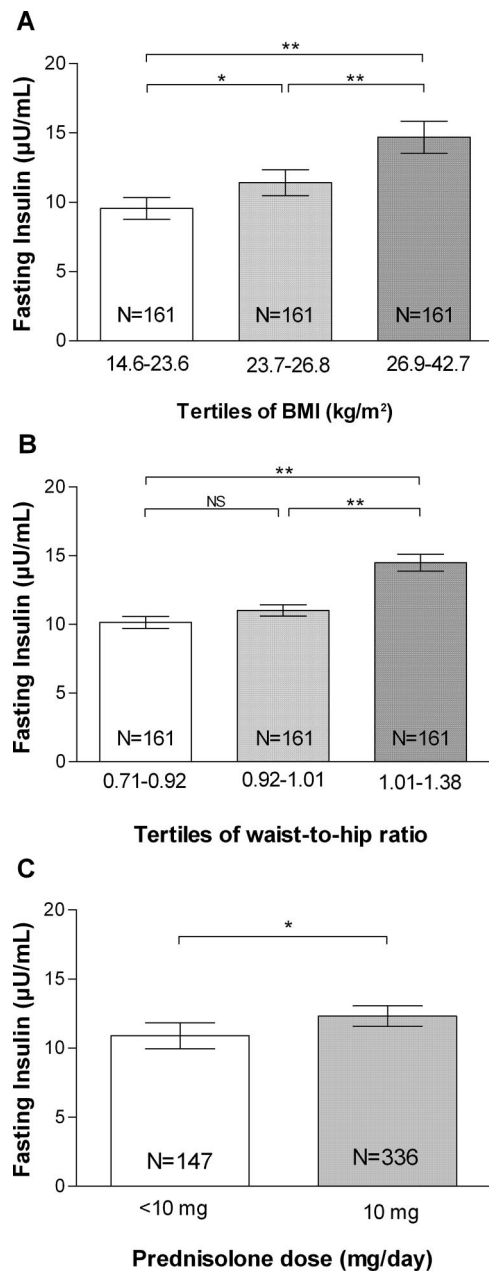


FIGURE 1. Determinants of fasting insulin concentrations. (A) Tertiles of body mass index. (B) Tertiles of waist-to-hip ratio. (C) Prednisolone dose. Results were similar for Homeostasis Model Assessment and McAuley's index. NS indicates not significant, * $P < 0.05$, ** $P < 0.001$. Tested with Mann-Whitney test.

C-reactive protein concentrations, was only associated with McAuley's index ($\beta = -0.10$, $P = 0.03$).

Table 2 also shows that in general, transplant-related characteristics were not associated with insulin resistance with the exception of prednisolone dose, which was univariately associated with all three indices. Figure 1C shows that fasting insulin concentrations increase with higher prednisolone dose. Renal allograft function, as reflected by creatinine clearance, was significantly associated with both fasting insulin concentrations and HOMA. This was also true for

creatinine excretion, a marker of muscle mass. McAuley's index was associated with serum creatinine. Previous CMV infection and use of tacrolimus tended to be associated with McAuley's index, but did not reach statistical significance. Other transplant-related characteristics did not show any association or any gender interaction.

Table 3 shows the factors that were independently associated with the insulin resistance indexes. Independent determinants for all three indexes were both obesity (BMI) and central obesity (waist-to-hip ratio), prednisolone dose, male gender, recipient age, HDL cholesterol, and total cholesterol. Other determinants differed among the indices. The univariate interaction between gender and BMI did not remain statistically significant in multivariate analyses for McAuley's index. Triglyceride concentrations and creatinine clearance were independently associated with HOMA and fasting insulin concentrations, respectively.

Regression analyses were repeated without inclusion of lipid concentrations and use of statins, because triglyceride concentrations are incorporated in McAuley's index (model 2). This could bias the analyses in model 1 toward an association with HDL cholesterol owing to the close relationship between HDL cholesterol and triglycerides. However, the adjusted analyses showed similar results as the primary analysis with the exception that tacrolimus use was independently associated with HOMA. Tolerance coefficients indicated that the assumption of colinearity was not violated in all models.

DISCUSSION

We investigated which recipient- and transplant-related factors were associated with insulin resistance in renal transplant recipients long term after transplantation. As judged from the magnitude of the standardized regression coefficients, the most important and consistent factors associated with insulin resistance were BMI, waist-to-hip ratio, and current prednisolone dose. Also independently associated were male gender, recipient age, HDL cholesterol, total cholesterol, and renal function. No independent associations were present for many transplant-related factors such as donor characteristics, acute rejection treatment, and CMV seropositivity.

Our results indicate that obesity is the most important determinant of insulin resistance in renal transplant recipients, as it is in the general population (22). This is important because trends in the epidemic of obesity among the general population are paralleled by the renal transplant population (23). The majority (60%) of transplant recipients in the United States are currently overweight or obese at the time of transplantation. Furthermore, many renal transplant recipients experience a 10% weight gain after transplantation (24), predominantly because of an increase in fat mass (25).

Not only was overall obesity (BMI) a determinant of insulin resistance, we also found that the distribution of obesity (waist-to-hip ratio) is an independent determinant of insulin resistance, even after adjustment for overall obesity. A possible explanation for waist-to-hip ratio as a determinant next to BMI could be because it better reflects the abdominal fat, which is thought to cause insulin resistance.

Another important determinant of insulin resistance was prednisolone dose. Midtvedt et al. (26) showed that lowering prednisolone dose toward 5 mg per day decreased insu-

TABLE 3. Multivariate regression analyses of independent determinants of fasting insulin, Homeostasis Model Assessment, and McAuley's index

Characteristics	Fasting insulin		Homeostasis Model Assessment		McAuley's index	
	β	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> value
Model 1						
Age, years	-0.21	<0.001	-0.20	<0.001	0.16	<0.001
Male gender	-0.20	<0.001	-0.15	0.002	0.19	<0.001
Body mass index, kg/m ²	0.26	<0.001	0.28	<0.001	-0.19	<0.001
Waist-to-hip ratio	0.29	<0.001	0.27	<0.001	-0.33	<0.001
Total cholesterol, mmol/L	-0.09	0.02	-0.13	0.004	-0.20	<0.001
High-density lipoprotein cholesterol, mmol/L	-0.11	0.001	-0.09	0.04	0.34	<0.001
Triglycerides, mmol/L			0.09	0.05		
Statin use, %					-0.16	<0.001
Creatinine clearance, ml/min	0.08	0.048				
Prednisolone dose, mg/d	0.10	0.015	0.09	0.026	-0.07	0.045
<i>R</i> ² , %		30		29		39
Model 2						
Age, years	-0.24	<0.001	-0.22	<0.001	0.21	<0.001
Male gender	-0.18	<0.001	-0.15	0.002	0.15	0.001
Body mass index, kg/m ²	0.26	<0.001	0.28	<0.001	-0.25	0.001
Waist-to-hip ratio	0.34	<0.001	0.35	<0.001	-0.45	<0.001
Creatine clearance, ml/min	0.09	0.038			0.08	0.038
Prednisolone dose, mg/d	0.10	0.011	0.09	0.038		
Tacrolimus use, %			0.08	0.049		
<i>R</i> ² , %		27		27		31

Betas are reported as standardized betas.

Model 1 is the full model. Model 2 was repeated without lipid concentrations and without statin use.

lin resistance. Our data are in accordance with this because recipients using <10 mg per day compared with 10 mg per day were less insulin-resistant. Studies indicate that tacrolimus is an independent risk factor for posttransplant diabetes (27), but in our study, only in model 2, HOMA was associated with tacrolimus use. This could be because tacrolimus is beta-cell toxic, decreasing insulin secretion more than increasing insulin resistance (28).

Some characteristics that were not associated with insulin resistance in our study are also important to note. Especially transplant-related characteristics have been suggested to explain why transplant recipients are more insulin-resistant than BMI- and age-matched nontransplant subjects. CMV is of particular interest in this respect, because shortly after transplantation, active CMV disease has been associated with insulin resistance (5). We found that CMV seropositivity does not determine insulin resistance longer after transplantation. Possibly, CMV infection shortly after hospitalization reduces physical activity of the recipient either because of malaise or because of the fact that the obligatory intravenous treatment with ganciclovir restricts mobility of a patient. Also, CMV causes inflammation, and inflammation has been shown to cause insulin resistance (29).

We also found creatinine clearance positively associated with fasting insulin concentrations and McAuley's index. The positive association between insulin resistance and

renal function is by itself not a new finding because glomerular filtration rate is known to increase under hyperinsulinemic conditions in nontransplanted kidneys (30). Possibly, this phenomenon is also present in transplanted kidneys.

Male gender was associated with less insulin resistance than female gender in multivariate analyses, but not in univariate analyses. This is a discrepancy that we cannot fully explain. It should be noted that women were more obese but that BMI had a greater impact on McAuley's index in men than in women. This could explain why there was no gender difference in insulin resistance. However, the gender and BMI interaction did not retain statistical significance in the multivariate model. Physiologically, it has been suggested that a gender difference in insulin resistance could be the result of different effects of sex hormones on body fat distribution and fat cell size (31).

A limitation of the present study is that insulin resistance was not measured with the hyperinsulinemic euglycemic clamp technique, but with indices based on fasting blood samples. However, the indices used have recently been validated in renal transplant recipients (10). Another limitation is that some known determinants of insulin resistance could not be taken into account such as free fatty acids, birth weight, or genetic factors, because we did not have information on these variables (21, 32).

It is important to know what the predominant determinants of insulin resistance are to reduce insulin resistance

in renal transplant recipients. With reduction of insulin resistance, renal transplant recipients could possibly experience less cardiovascular morbidity and less chronic transplant dysfunction (33). In analogy to the general population, reduction of insulin resistance could perhaps be achieved by weight management. Furthermore, tapering of prednisolone dose could decrease insulin resistance as well, but prednisone withdrawal negatively impacts long-term graft failure (34).

In conclusion, this study shows that obesity, the distribution of obesity, and prednisolone dose are predominant determinants of insulin resistance long term after transplantation. Second, male gender, recipient age, HDL cholesterol and total HDL cholesterol concentrations, and creatinine clearance were also independent determinants of insulin resistance. Transplant-related characteristics such as CMV status did not determine insulin resistance long term after renal transplantation. Insulin resistance after renal transplantation, and perhaps cardiovascular mortality, may be managed favorably by weight reduction and prednisolone dose reduction.

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